
Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

EVIDENCE PROFILES

- Tobacco cessation
- Weight management
- Substance use disorders
- Cardiovascular disease and cardiovascular risk
- Diabetes mellitus
- HIV/AIDS
- Other infectious diseases (Tuberculosis, Hepatitis A/B)



**World Health
Organization**

EVIDENCE PROFILE

TOBACCO CESSATION

PICO QUESTION: For people with severe mental disorder (SMD) who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

Background on the PICO question

The majority of deaths amongst people with SMD are attributable to physical diseases. People with SMD are also more likely to engage in lifestyle behaviours, which increase the risk of developing physical illnesses. Tobacco use is one of these lifestyle behaviours that is common amongst people with SMD. People with SMD are twice as likely to smoke as the general population (around 61% of people with SMD smoke compared to 33% in the general population), to smoke more on average, and are less likely to quit smoking (CDC 2015). Tobacco use has therefore been identified as a leading preventable cause of premature mortality in this population. People with SMD have been reported to die 15-20 years earlier on average than people in the general population and this is often due to preventable smoking-related health conditions (Trainor & Leavey 2017), for example due to heart disease, cancer, and lung disease, which can all be caused by smoking. Nicotine has also been shown to have mood-altering effects that can temporarily mask the negative symptoms of mental illness, putting people with mental illness at higher risk for cigarette use and nicotine addiction, and tobacco smoke can interact with and inhibit the effectiveness of certain medications taken by mental health and substance abuse patient (<https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.html>).

In regards to interventions that have been recommended in the general population for tobacco cessation, bupropion, varenicline and nicotine replacement therapy (NRT) have all been recommended (e.g. mhGAP Intervention Guide, NICE), and NICE has also recommended these pharmacological interventions for tobacco cessation for people with mental disorders.

This document covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD who use tobacco. Those outcomes were included, which were considered to be critical or important tobacco-cessation-related outcomes.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Population: People with SMD who use tobacco

Intervention:

- Pharmacological interventions: including nicotine replacement therapy (NRT), bupropion, varenicline
- Non-pharmacological interventions

Comparison: care as usual and/or placebo

Outcomes:

- Critical
 - Tobacco cessation/abstinence rates
 - Tobacco consumption rates
 - Respiratory disease outcomes (COPD, asthma)
- Important:
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18

Roberts E et al. Efficacy and acceptability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis. Addiction. 2016; 111(4): 599-612

Secades-Villa R et al. Psychological, pharmacological, and combined smoking cessation interventions for smokers with current depression: A systematic review and meta-analysis. PloS one. 2017; 12(12): e0188849

Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253

EXCLUDED FROM GRADE TABLES

Ahmed AIA et al. Neuropsychiatry adverse events of varenicline: A systematic review of published reports. Journal of Clinical Psychopharmacology. 2013; 33(1): 55-62

Aldi GA et al. Effectiveness of pharmacological or psychological interventions for smoking cessation in smokers with major depression or depressive symptoms: A systematic review of the literature. Substance abuse. 2018

Bennett ME et al. Smoking cessation in people with schizophrenia. 2013; 6(3): 180-190

Cooper SJ et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol. 2016; 30(8): 717-48

Englisch S et al. Risks and benefits of bupropion treatment in schizophrenia: a systematic review of the current literature. Clin Neuropharmacol. 2013; 36(6): 203-215

Evins AE et al. Treatment of tobacco use disorders in smokers with serious mental illness: toward clinical best practices. Harv Rev Psychiatry. 2015; 23(2): 90-98

Galling, B & Correll, C U. Antidepressant augmentation of antipsychotics in schizophrenia: A systematic review, meta-analysis and metaregression analysis. European Neuropsychopharmacology. 2017; 27(S4): S946-S947

Hartmann-Boyce J et al. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. Addiction. 2014; 109(9): 1414-25

- Hughes JR. Varenicline as a cause of suicidal outcomes. *Nicotine and Tobacco Research*. 2016; 18(1): 2-9
- Khanna P et al. Smoking cessation advice for people with serious mental illness. *Cochrane Database of Systematic Reviews*. 2016; 1: CD009704
- Kishi T & Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2015; 265(3): 259-268
- Kuipers E et al. Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. *BMJ*. 2014; 348: g1173
- Muehlig S et al. Psychiatric comorbidities with tobacco-related disorders. *Nervenarzt*. 2016; 87(1): 46-52
- Rodrigues C et al. Varenicline suicidal ideation in psychiatric patients-a case report and systematic review. *European Neuropsychopharmacology*. 2016; 26(S2): S710
- Ruether T et al. EPA guidance on tobacco dependence and strategies for smoking cessation in people with mental illness. *European Psychiatry*. 2014; 29(2): 65-82
- Sharma R et al. An appraisal of practice guidelines for smoking cessation in people with severe mental illness. *Australian and New Zealand Journal of Psychiatry*. 2017; 51(11): 1106-1120
- Stubbs B et al. How can we promote smoking cessation in people with schizophrenia in practice? A clinical overview. *Acta Psychiatr Scand*. 2015; 132(2): 122-30
- Van de Meer RM et al. Smoking cessation interventions for smokers with current or past depression. *Cochrane Database of Systematic Reviews*. 2013; 8(8): CD006102
- Van Hasselt FM et al. Evaluating interventions to improve somatic health in severe mental illness: A systematic review. *Acta Psychiatrica Scandinavica*. 2013; 128(4): 251-260
- Wilson A et al. A systematic narrative review of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups (2010-2017). *Expert Review of Respiratory Medicine*. 2017; 11(8): 617-630
- Wu IH & Abughosh S. Smoking cessation pharmacological interventions among schizophrenia smokers-a systematic review. *Value in Health*. 2014; 2014; 17(3): A170
- Wu Q et al. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. *Addiction*. 2016; 111(9): 1154-1167

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Bupropion vs. placebo	Tobacco cessation/abstinence rates	Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD, and it provides analyses for three different time points.
		Tobacco consumption rates	Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253	Most recent high-quality systematic review (Cochrane) that assessed tobacco consumption rates; however it is 5 years old and for schizophrenia only (rather than SMD overall).
		Respiratory disease outcomes (COPD, asthma)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Roberts E et al. Efficacy and acceptability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis. Addiction. 2016; 111(4): 599-612	Most recent high-quality systematic review for people with SMD that has conducted meta-analysis for adverse events.
2	Varenicline vs. placebo	Tobacco cessation/abstinence rates	Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD.
		Tobacco consumption rates	Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253	Most recent high-quality systematic review (Cochrane) that assessed tobacco consumption rates; however it is 5 years old and for

				schizophrenia only (rather than SMD overall).
		Respiratory disease outcomes (COPD, asthma)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Roberts E et al. Efficacy and acceptability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis. <i>Addiction</i> . 2016; 111(4): 599-612	Most recent high-quality systematic review for people with SMD that has conducted meta-analysis for adverse events.
3	Nicotine replacement therapy (NRT) vs. placebo	Tobacco cessation/abstinence rates	Secades-Villa R et al. Psychological, pharmacological, and combined smoking cessation interventions for smokers with current depression: A systematic review and meta-analysis. <i>PloS one</i> . 2017; 12(12): e0188849	Most recent high-quality systematic review on NRT (as NRT is not sufficiently covered by Peckham et al 2017), though it looks at depression rather than SMD (no recent suitable systematic review available for SMD).
		Tobacco consumption rates	Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. <i>Cochrane Database of Systematic Reviews</i> . 2013; 2(2): CD007253	Most recent high-quality systematic review (Cochrane) that assessed tobacco consumption rates; however it is 5 years old and for schizophrenia only (rather than SMD overall).
		Respiratory disease outcomes (COPD, asthma)	No relevant systematic review available.	N/A
		Frequency of adverse events / side-effects	No relevant systematic review available.	N/A
4	Specialised smoking cessation interventions vs. standard smoking cessation interventions	Tobacco cessation/abstinence rates	Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. <i>BMC Psychiatry</i> . 2017; 17: 18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD.
		Tobacco consumption	No relevant systematic review available.	N/A

		rates		
		Respiratory disease outcomes (COPD, asthma)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD.
5	Contingent reinforcement vs. care as usual	Tobacco cessation/abstinence rates	Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD.
		Tobacco consumption rates	Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253	Most recent high-quality systematic review (Cochrane) that assessed tobacco consumption rates; however it is 5 years old and for schizophrenia only (rather than SMD overall).
		Respiratory disease outcomes (COPD, asthma)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A

Narrative description of the studies that went into analysis¹

Peckham et al (2017) conducted an update to a systematic review that aimed to assess the effectiveness and cost-effectiveness of smoking cessation and reduction strategies in adults with severe mental ill health in both inpatient and outpatient settings. Electronic databases were searched during September 2016 for randomised controlled trials comparing smoking cessation interventions to each other, usual care, or placebo. 26 trials of pharmacological and/or behavioural interventions were included. Eight trials comparing bupropion to placebo were pooled showing that bupropion improved quit rates significantly in the medium and long term but not the short term (short term RR = 6.42 95% CI 0.82–50.07; medium term RR = 2.93 95% CI 1.61–5.34; long term RR = 3.04 95% CI 1.10–8.42). Five trials comparing varenicline to placebo showed that the addition of varenicline improved quit rates significantly in the medium term (RR = 4.13 95% CI 1.36–12.53). The results from five trials of specialised smoking cessation programmes were pooled and showed no evidence of benefit in the medium (RR = 1.32 95% CI 0.85–2.06) or long term (RR = 1.33 95% CI 0.85–2.08). There was insufficient data to allowing pooling for all time points for varenicline and trials of specialist smoking cessation programmes. Trials suggest few adverse events although safety data were not always reported. Only one pilot study reported cost effectiveness data. Authors' conclusions: Bupropion and varenicline, which have been shown to be effective in the general population, also work for people with severe mental ill health and their use in patients with stable psychiatric conditions.

Roberts et al (2016) conducted a systematic review and network meta-analysis. Databases were searched on 1 December 2014 for randomised controlled trials (RCTs) published in English. All studies were included of smokers with SMI (including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder and depressive psychoses) who were motivated to quit smoking. Pharmacotherapies included nicotine replacement therapy (NRT), bupropion and varenicline delivered as monotherapy or in combination compared with each other or placebo. The efficacy outcome was self-reported sustained smoking cessation, biochemically verified at the longest reported time point. The tolerability outcome was number of patients discontinuing the trial due to any adverse event. Results: Seventeen study reports were included which represented fourteen individual RCTs. No trials were found in patients with depressive psychoses, delusional disorder or which compared NRT monotherapy with placebo. A total of 356 and 423 participants were included in the efficacy and tolerability analyses respectively. From the network meta-analysis both bupropion and varenicline were more effective than placebo (OR 4.51 95% Credible Interval (CrI) 1.45 to 14.04 and OR 5.17 95% CrI 1.78 to 15.06 respectively). Data were insensitive to an assessment of varenicline versus bupropion (OR 1.15 95% CrI 0.24 to 5.45). There were no significant differences in tolerability. All outcomes were rated by GRADE criteria as very low quality. Authors' conclusions: The limited evidence available to date suggests that bupropion and varenicline are effective and acceptable for smoking cessation in adults with serious mental illnesses.

Secades-Villa et al (2017) conducted a systematic literature review and meta-analysis of smoking cessation interventions for patients with current depression. Of the 6,584 studies identified, 20 were eligible and included in the review. Trial designs of studies were 16 randomized controlled trials and 4 secondary studies. Studies included three types of intervention: psychological (6/30%), pharmacological (6/30%) or combined (8/40%). Four trials comprised special populations of smokers. Four studies received a strong methodological quality, 7 were scored as moderate and 9 studies received a weak methodological rating. Analyses of effectiveness showed that smoking cessation interventions appear to increase short-term and long-term smoking abstinence in individuals with current depression. Subgroup analyses revealed stronger effects among studies that provided pharmacological treatments than in studies using psychological treatments. However, the evidence is weak due to the small number of studies. Smoking abstinence appears to be associated with an improvement in depressive symptoms. Heterogeneity in protocols in similar types of treatment

¹ Please note that this section includes the abstracts as taken directly from the publications.

also prevent firm conclusions being drawn on the effectiveness of any particular treatment model to optimally manage abstinence among depressed smokers. Further research is required to strengthen the evidence base.

Tsoi et al (2013) conducted a Cochrane systematic review, to evaluate the benefits and harms of different treatments for nicotine dependence in schizophrenia. Randomised trials for smoking cessation or reduction were included, comparing any pharmacological or non-pharmacological intervention with placebo or with another therapeutic control in adult smokers with schizophrenia or schizoaffective disorder. 34 trials were included (16 trials of cessation; nine trials of reduction; one trial of relapse prevention; eight trials that reported smoking outcomes for interventions aimed at other purposes). Seven trials compared bupropion with placebo; meta-analysis showed that cessation rates after bupropion were significantly higher than placebo at the end of treatment (seven trials, N = 340; risk ratio [RR] 3.03; 95% confidence interval [CI] 1.69 to 5.42) and after six months (five trials, N = 214, RR 2.78; 95% CI 1.02 to 7.58). There were no significant differences in positive, negative and depressive symptoms between bupropion and placebo groups. There were no reports of major adverse events such as seizures with bupropion. Smoking cessation rates after varenicline were significantly higher than placebo, at the end of treatment (2 trials, N = 137; RR 4.74, 95% CI 1.34 to 16.71). Only one trial reported follow-up at six months and the CIs were too wide to provide evidence of a sustained effect (one trial, N = 128, RR 5.06, 95% CI 0.67 to 38.24). There were no significant differences in psychiatric symptoms between the varenicline and placebo groups. Nevertheless, there were reports of suicidal ideation and behaviours from two people on varenicline. Two studies reported that contingent reinforcement (CR) with money may increase smoking abstinence rates and reduce the level of smoking in patients with schizophrenia. However, it is uncertain whether these benefits can be maintained in the longer term. There was no evidence of benefit for the few trials of other pharmacological therapies (including nicotine replacement therapy (NRT)) and psychosocial interventions in helping smokers with schizophrenia to quit or reduce smoking. The authors concluded that bupropion increases smoking abstinence rates in smokers with schizophrenia, without jeopardizing their mental state. Varenicline may also improve smoking cessation rates in schizophrenia, but its possible psychiatric adverse effects cannot be ruled out. CR may help this group of patients to quit and reduce smoking in the short term. The authors failed to find convincing evidence that other interventions have a beneficial effect on smoking in schizophrenia.

GRADE Evidence Tables²

Table 1: Bupropion vs. placebo for people with SMD who use tobacco

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Bupropion compared to placebo for people with SMD who use tobacco

Setting: mental health inpatients and outpatients

Bibliography:

Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18

Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253

Roberts E et al. Efficacy and acceptability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis. Addiction. 2016; 111(4): 599-612

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	bupropion	placebo	Relative (95% CI)	Absolute (95% CI)		
Tobacco cessation/abstinence rates (RR above 1 favours bupropion) (follow up: median 4 weeks)												
2 ^a	randomised trials	serious ^b	not serious ^c	not serious	very serious _d	none detected ^e	5/34 (14.7%)	0/37 (0.0%)	RR 6.42 (0.82 to 50.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
Tobacco cessation/abstinence rates (RR above 1 favours bupropion) (follow up: median 3.5 months)												

² See Annex 5, page XX for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	bupropion	placebo	Relative (95% CI)	Absolute (95% CI)		
7 ^t	randomised trials	very serious ^g	not serious ^c	not serious	not serious	none detected ^e	34/130 (26.2%)	11/133 (8.3%)	RR 2.93 (1.61 to 5.34)	160 more per 1,000 (from 50 more to 359 more)	⊕⊕○○ LOW	CRITICAL
Tobacco cessation/abstinence rates (RR above 1 favours bupropion) (follow up: median 11.75 months)												
4 ⁿ	randomised trials	very serious ⁱ	not serious ^c	not serious	serious ^j	none detected ^e	13/79 (16.5%)	4/80 (5.0%)	RR 3.04 (1.10 to 8.42)	102 more per 1,000 (from 5 more to 371 more)	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - expired CO level (ppm) at end of treatment (MD below 0 favours bupropion)												
4 ^k	randomised trials	serious ^l	not serious ^m	serious ⁿ	serious ^o	none detected ^p	84	85	-	MD 6.8 lower (10.79 lower to 2.81 lower) ^q	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - expired CO level (ppm) at 6-month follow-up (MD below 0 favours bupropion)												
3 ^r	randomised trials	serious ^s	very serious ^t	serious ⁿ	very serious ^u	none detected ^p	60	63	-	MD 5.55 lower (17.89 lower to 6.78 higher) ^v	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - change in number of CPD at end of treatment abstinence studies (MD below 0 favours bupropion)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	bupropion	placebo	Relative (95% CI)	Absolute (95% CI)		
3 ^w	randomised trials	serious ^x	not serious ^y	serious ⁿ	serious ^z	none detected ^p	90	94	-	MD 10.77 lower (16.52 lower to 5.01 lower) ^{aa}	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - change in number of CPD at 6-month follow-up abstinence studies (MD below 0 favours bupropion)												
2 ^{ab}	randomised trials	serious ^{ac}	not serious ^{ad}	serious ⁿ	very serious ^{ae}	none detected ^p	50	54	-	MD 0.4 higher (5.72 lower to 6.53 higher)	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - change in number of CPD at end of treatment reduction studies (MD below 0 favours bupropion)												
2 ^{at}	randomised trials	very serious ^{ag}	not serious ^{ah}	serious ⁿ	very serious ^{ae}	none detected ^p	61	32	-	MD 2.61 lower (7.99 lower to 2.77 higher) ^{ai}	⊕○○○ VERY LOW	CRITICAL
Respiratory disease outcomes - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events / side-effects (number of participants who discontinued the trial because of adverse events) (OR below 1 favours bupropion)												
6 ^{aj}	randomised trials	very serious ^{ak}	not serious ^{al}	not serious	serious ^{am}	none detected ^{an}	6/114 (5.3%)	6/87 (6.9%)	OR 0.93 (0.18 to 4.74)	5 fewer per 1,000 (from 56 fewer to 191 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. Both studies were conducted in the US. One of them compared bupropion + CBT vs. placebo + CBT, and the other compared bupropion + behavioural therapy intervention vs. placebo + behavioural therapy intervention. All participants had either schizophrenia or schizoaffective disorder, and were also taking anti-psychotics. See Table 1 in Peckham et al 2017.
- b. This has been rated as serious, as both studies had an unclear risk of bias for masking of outcome assessment. See Table 2 in Peckham et al 2017.
- c. Heterogeneity (I²) was reported to be 0%. See Fig. 2 of Peckham et al 2017.
- d. This has been rated as very serious, as the number of participants is very low (i.e. under 100 participants in total), the confidence interval includes 'no effect' and there is indication of appreciable benefit.
- e. The authors of the systematic review (Peckham et al 2017) did not perform funnel plots because less than 10 studies were eligible for inclusion into the meta-analyses. However, the authors of the systematic review checked trial registries to determine whether there were any trials registered that had not been published, and did not report any suspected publication bias (see page 17 of Peckham et al 2017).
- f. All 7 studies were conducted in the US. Participants in 6 studies had either schizophrenia or schizoaffective disorder, and bipolar disorder in 1 study. All studies compared bupropion to placebo, plus one of the following interventions (the same interventions were always used in the bupropion and placebo groups): CBT; (group) behavioural therapy (+ NRT patch); nicotine patch/gum and CBT; specialised smoking cessation programme; group support programme. See Table 1 in Peckham et al 2017.
- g. This has been rated as very serious, as 6 of the 7 included studies had an unclear risk of bias for masking of outcome assessment, and at least 2 of the studies had a drop-out rate of above 30%. This information was taken from Table 2 in Peckham et al 2017 and from the individual studies included in the systematic review.
- h. All 4 studies were conducted in the US. All participants had either schizophrenia or schizoaffective disorder. All studies compared bupropion to placebo, plus one of the following interventions (the same interventions were always used in the bupropion and placebo groups): CBT; group behavioural therapy + NRT patch; nicotine patch/gum and CBT; specialised smoking cessation programme. See Table 1 in Peckham et al 2017.
- i. This has been rated as very serious, as 3 of the 4 studies had an unclear risk of bias for masking of outcome assessment, and 1 study had a drop-out rate of above 30%. This information was taken from Table 2 in Peckham et al 2017 and from the individual studies included in the systematic review.
- j. This has been rated as serious, as the total number of participants is low (i.e. between 100 and 200). See Figure 2 in Peckham et al 2017.
- k. Please note that this systematic review (Tsoi et al 2013) was published 5 years ago and included only participants with schizophrenia or schizoaffective disorder. All studies were conducted in the US. In 3 of the studies, participants in both groups also received CBT, and in 1 study they also received group therapy.
- l. This has been rated as serious, as 2 of the 4 studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from the 'characteristics of studies' tables in Tsoi et al 2013.
- m. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% (see Analysis 1.4 in Tsoi et al 2013).
- n. This has been rated as serious, as the systematic review only included people with schizophrenia or schizoaffective disorder, and the study is five years old.
- o. This has been rated as serious, as the total number of participants is low (see Analysis 1.4 in Tsoi et al 2013).
- p. No publication bias was detected by the authors of the systematic review (Tsoi et al 2013), though funnel plots could not be produced due to the low number of studies.
- q. This information was taken from Analysis 1.4 in Tsoi et al 2013.
- r. Please note that this systematic review (Tsoi et al 2013) was published 5 years ago and included only participants with schizophrenia or schizoaffective disorder. All studies were conducted in the US and all participants in both groups also received CBT.

- s. This has been rated as serious, as 1 of the studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from the 'characteristics of studies' tables in Tsoi et al 2013.
- t. This has been rated as very serious, as heterogeneity (I²) was reported to be 86% (see Analysis 1.5 in Tsoi et al 2013).
- u. This has been rated as very serious, as the total number of participants is low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.
- v. This information was taken from Analysis 1.5 in Tsoi et al 2013.
- w. Please note that this systematic review (Tsoi et al 2013) was published 5 years ago and included only participants with schizophrenia or schizoaffective disorder. 2 studies were conducted in the US, and 1 in China. In 2 of the studies, participants in both groups also received CBT.
- x. This has been rated as serious, as 2 of the studies had an unclear risk of bias for masking of outcome assessment and drop-out rate (information taken from the 'characteristics of studies' tables in Tsoi et al 2013).
- y. This was rated as 'not serious', as heterogeneity (I²) was reported to be 40% by Tsoi et al (2013) (see Analysis 1.6).
- z. This has been rated as serious, as the number of participants is low.
- aa. This information was taken from Analysis 1.6 in Tsoi et al 2013.
- ab. Please note that this systematic review (Tsoi et al 2013) was published 5 years ago and included only participants with schizophrenia or schizoaffective disorder. Both studies were conducted in the US. In both of the studies, participants in both groups also received CBT.
- ac. This has been rated as serious, as 1 of the studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from the 'characteristics of studies' tables in Tsoi et al 2013.
- ad. This has been rated as 'not serious', as heterogeneity (I²) was reported to be 0% by Tsoi et al (2013) (see Analysis 1.7).
- ae. This has been rated as very serious, as the number of participants is low, and the confidence interval includes 'no effect' and appreciable benefit and harm.
- af. Please note that this systematic review (Tsoi et al 2013) was published 5 years ago and included only participants with schizophrenia or schizoaffective disorder. One study was conducted in Iran and one in Israel. In one study both groups also received CBT.
- ag. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from the 'characteristics of studies' tables in Tsoi et al 2013.
- ah. This was rated as 'not serious', as heterogeneity (I²) was reported to be 0% by Tsoi et al (2013) (see Analysis 1.8).
- ai. This information was taken from Analysis 1.8 in Tsoi et al 2013.
- aj. 5 studies were conducted in the US, and one in Israel. Participants in 5 studies had either schizophrenia or schizoaffective disorder, and bipolar disorder in the remaining study. All studies compared bupropion to placebo, plus one of the following interventions (the same interventions were always used in the bupropion and placebo groups): CBT; (group) behavioural therapy; group support programme; counselling. This information was taken from Roberts et al 2016.
- ak. This has been rated as very serious, as all 6 studies had an unclear risk of bias for masking of outcome assessment, and 2 studies had a drop-out rate of above 30% (and a further study had a drop-out rate of 29.2%). This information was taken from the individual studies included in the systematic review.
- al. This has been rated as not serious, as heterogeneity (I²) was reported to be 26% by Robert et al 2016 (see Figure S4).
- am. This has been rated as serious, as the confidence interval includes 'no effect' and there is indication of appreciable benefit and harm.
- an. The authors of the systematic review (Robert et al 2016) reported no publication bias (see Figure S9).

Table 2: Varenicline vs. placebo for people with SMD who use tobacco

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Varenicline compared to placebo for people with SMD who use tobacco

Setting: mental health inpatients and outpatients

Bibliography:

Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18

Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253

Roberts E et al. Efficacy and acceptability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis. Addiction. 2016; 111(4): 599-612

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	varenicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Tobacco cessation/abstinence rates (RR above 1 favours varenicline) (follow up: median 6 months)												
4 ^a	randomised trials	serious ^b	not serious ^c	not serious	serious ^d	none detected ^e	19/122 (15.6%)	3/78 (3.8%)	RR 4.13 (1.36 to 12.53)	120 more per 1,000 (from 14 more to 443 more)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	varenicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Tobacco consumption rates												
2 ^f	randomised trials	serious ^g	not serious	serious ^h	serious ⁱ	none detected ^j	Williams (2012) (n=128; cross-over design) found that for non-abstinent participants, there was a statistically significant reduction of cigarettes per day (CPD) from baseline, in favour of the varenicline group at week 12, who smoked three fewer CPD compared to the placebo group (95% CI 0.4 to 6.1, P = 0.03). The result was no longer significant at week 24. However, non-abstainers in both groups had reduced levels of expired carbon monoxide (CO) level at week 12, but the difference was not statistically significant (P = 0.11). In Weiner (2011) (n=9; cross-over design) from week four onwards the varenicline group showed a significantly greater reduction of expired CO from baseline compared to the placebo group (P = 0.02), although it was unclear whether this result included those who managed to abstain from smoking.				⊕○○○ VERY LOW	CRITICAL
Respiratory disease outcomes - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events / side-effects (number of participants who discontinued the trial because of adverse events) (OR below 1 favours varenicline)												
5 ^k	randomised trials	very serious ^l	not serious ^m	not serious	serious ⁿ	none detected ^o	14/131 (10.7%)	7/91 (7.7%)	OR 1.29 (0.47 to 3.56)	20 more per 1,000 (from 39 fewer to 152 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. 2 of the 4 studies were conducted in the US, 1 in Canada, and 1 in Canada and the US. Participants in 2 of the studies included people with schizophrenia or schizoaffective disorder, and 2 studies included people with bipolar disorder. 3 of the studies compared varenicline + smoking cessation counselling to placebo + smoking cessation counselling, and 1 study compared varenicline to placebo. See Table 1 in Peckham et al 2017.

- b. This has been rated as serious, as one of the studies had a drop-out rate of 40% (this was a very small study with only 5 participants; both people who dropped out were in the placebo arm), and 2 of the studies had an unclear risk of bias for masking of outcome assessment. This information was taken from Table 2 in Peckham et al 2017, and from the individual studies included in the systematic review.
- c. This was rated as not serious, as heterogeneity (I²) was reported to be 0% by Peckham et al 2017 (see Figure 3).
- d. This has been rated as serious, as the number of participants is low, particularly in the placebo group.
- e. The authors of the systematic review (Peckham et al 2017) did not perform funnel plots because less than 10 studies were eligible for inclusion into the meta-analyses. However, the authors checked trial registries to determine whether there were any trials registered that had not been published, and did not report any suspected publication bias (see page 17 in Peckham et al 2017).
- f. One of the studies was conducted in the US, and the other in the US and Canada. All participants had either schizophrenia or schizoaffective disorder. All participants (varenicline and placebo groups) also received counselling. Information taken from Tsoi et al 2013.
- g. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from the 'characteristics of studies' tables in Tsoi et al 2013.
- h. This has been rated as serious, as studies were included for schizophrenia, and the systematic review is more than 3 years old (timeliness criterion).
- i. This has been rated as serious, as the number of participants is low.
- j. Funnel plots were not produced by the authors of the systematic review (Tsoi et al 2013), as the number of studies was too small, so no publication bias was detected.
- k. All 5 studies were conducted in the US. 4 of the studies included participants with schizophrenia or schizoaffective disorder, and 1 study included people with bipolar disorder. 3 of the studies compared varenicline + smoking cessation counselling to placebo + smoking cessation counselling, 1 compared varenicline + motivational interviewing to placebo + motivational interviewing, and 1 compared varenicline to placebo. See Table 1 in Roberts et al 2016.
- l. This has been rated as very serious, as 3 of the 5 studies had an unclear risk of bias for masking of outcome assessment, and 1 study had a drop-out rate of above 30 % (a further study had a drop-out rate of 29.2%). This information was taken from the individual studies included in the systematic review.
- m. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Roberts et al 2016 (see Figure S6).
- n. This has been rated as serious, as the confidence interval includes 'no effect' and an appreciable level of benefit and harm.
- o. The authors of the systematic review (Roberts et al 2016) reported no publication bias (see Figure S10 in Roberts et al 2016).

Table 3: Nicotine replacement therapy vs. placebo for people with SMD who use tobacco

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Nicotine replacement therapy compared to placebo for people with SMD who use tobacco

Setting: not specified

Bibliography:

Secades-Villa R et al. Psychological, pharmacological, and combined smoking cessation interventions for smokers with current depression: A systematic review and meta-analysis. PloS one.2017; 12(12): e0188849

Tsoi DT et al. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2013; 2(2): CD007253

Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	nicotine replacement therapy	placebo	Relative (95% CI)	Absolute (95% CI)		
Tobacco cessation/abstinence rates (RR above 1 favours NRT) (follow up: 29 days)												
1 ^a	randomised trials	not serious	not serious	serious ^b	very serious ^c	none detected ^d	14/18 (77.8%)	10/20 (50.0%)	RR 1.56 (0.94 to 2.57)	280 more per 1,000 (from 30 fewer to 785 more)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	nicotine replacement therapy	placebo	Relative (95% CI)	Absolute (95% CI)		
Tobacco consumption rates												
2 ^e	randomised trials	serious ^f	serious ^g	not serious	serious ^h	none detected	Dalak 1999 found no significant difference between NRT (=10) and placebo (n=9) in terms of expired CO level and CPD, though the heaviest smokers had a statistically significant decrease in expired CO level of at least 20% (Tsoi et al 2013). There was no evidence of nicotine toxicity or significant side-effects, though people with NRT had more abnormal involuntary movement. Hartman 1991 found that participants smoked significantly fewer cigarettes while receiving NRT than while receiving placebo (n=10, mean number of cigarettes with nicotine = 10.5, mean number of cigarettes with placebo = 13.5, t = -3.21, df = 9, P < 0.05). Only those who smoked at least 12 cigarettes (approximately 1.8/hour) while wearing the placebo patch achieved benefit from the NRT patch.				⊕○○○ VERY LOW	CRITICAL
Respiratory disease outcomes - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events / side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The systematic review (Secades-Villa et al 2017) included studies with current depression, either defined as MDD or depressive symptoms. Whilst the systematic review identified two studies that assessed NRT, only the results of the study that included participants with MDD is included here. This was an RCT comparing nicotine patches to placebo patches (both groups with counselling), conducted in the US.

b. This has been rated as serious, as the study assessed smoking cessation in people with MDD rather than SMD.

c. This has been rated as very serious, as the total number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit.

d. No publication bias was detected by the authors of the systematic review (Secades-Villa et al 2017), though it could not be assessed through funnel plots due to the low number of studies.

- e. Both Peckham et (2017) and Tsoi et al (2013) identified the one same study that looked at consumption rates for NRT compared to placebo in people with schizophrenia in the USA. However, only Tsoi et al (2013) reported the results of this. Tsoi et al (2013) also conducted a sub-group analysis to look at this in a further study .
- f. This has been rated as serious, as both studies had an unclear risk of bias for masking of outcome assessment and drop-out rates. This information was taken from Peckham et al 2017 and Tsoi et al 2013.
- g. This has been rated as serious, as the two studies had different findings (though results were not pooled).
- h. This has been rated as serious, as the number of participants is low.

Table 4: Specialised smoking cessation interventions vs. standard smoking cessation interventions for people with SMD who use tobacco

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Specialised (for people with SMD) smoking cessation interventions compared to standard smoking cessation intervention for people with SMD who use tobacco

Setting: mental health outpatients

Bibliography: Peckham E et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017; 17: 18

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	specialised (for people with SMD) smoking cessation interventions	standard smoking cessation intervention	Relative (95% CI)	Absolute (95% CI)		
Tobacco cessation/abstinence rates (RR above 1 favours specialised smoking cessation interventions) (follow up: median 6 months)												
3 ^a	randomised trials	very serious ^b	serious ^c	not serious	serious ^d	none detected ^e	39/220 (17.7%)	26/210 (12.4%)	RR 1.32 (0.85 to 2.06)	40 more per 1,000 (from 19 fewer to 131 more)	⊕○○○ VERY LOW	CRITICAL
Tobacco cessation/abstinence rates (RR above 1 favours specialised smoking cessation interventions) (follow up: median 12 months)												
4 ^f	randomised trials	very serious ^g	not serious ^h	not serious	serious ^d	none detected ^e	37/253 (14.6%)	27/245 (11.0%)	RR 1.33 (0.85 to 2.08)	36 more per 1,000 (from 17 fewer to 119 more)	⊕○○○ VERY LOW	CRITICAL
Tobacco consumption rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Respiratory disease outcomes - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Frequency of adverse events / side-effects (follow up: 12 months)												
1 ⁱ	randomised trials	very serious ^j	not serious	not serious	serious ^k	none detected ^e	15/46 (32.6%)	6/51 (11.8%) _m	not estimable		⊕○○○ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. 2 of the studies were conducted in the USA, and 1 in Australia. All participants were diagnosed with a psychotic disorder (schizophrenia or schizoaffective disorder in 2 of the studies). All studies compared a specialised smoking cessation intervention (motivational enhancement / psychoeducation + NRT; motivational interviewing + NRT; motivational interviewing + CBT + NRT) to standard care (group counselling + NRT; active education + NRT; motivational interviewing + CBT + NRT). See Table 1 in Peckham et al 2017.
- b. This has been rated as very serious, as 1 of the 3 studies had a very high drop-out rate and an unclear risk of bias for masking of outcome assessment. This information was taken from Table 2 in Peckham et al 2017, and from the individual studies included in the systematic review.
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 70% by Peckham et al 2017 (see Figure 4).
- d. This has been rated as serious, as the confidence interval includes 'no effect' and an indication of appreciable benefit.
- e. The authors of the systematic review (Peckham et al 2017) did not perform funnel plots because less than 10 studies were eligible for inclusion into the meta-analyses. However, the authors checked trial registries to determine whether there were any trials registered that had not been published, and did not report any suspected publication bias (see page 17 in Peckham et al 2017).
- f. 2 of the studies were conducted in the US, 1 in Australia, and 1 in the UK. All participants were diagnosed with a psychotic disorder (schizophrenia or schizoaffective disorder, or bipolar disorder). All studies compared a specialised smoking cessation intervention (motivational enhancement / psychoeducation + NRT; motivational interviewing + NRT; motivational interviewing + CBT + NRT; behavioural support + drugs) to standard care (group counselling + NRT; active education + NRT; motivational interviewing + CBT + NRT; advice and usual care). See Table 1 in Peckham et al 2017.
- g. This has been rated as very serious, as 2 of the studies had drop-out rates of above 30%, and 1 of the studies had a high risk and another study had an unclear risk for masking of outcome assessment. This information was taken from Table 2 in Peckham et al 2017 and from the individual studies included in the systematic review.
- h. This was rated as not serious, as heterogeneity (I²) was reported to be 0% by Peckham et al 2017 (see Figure 4).
- i. Only one of the studies on specialised smoking cessation interventions included in the systematic review (Peckham et al 2017) reported on serious adverse events. This study was conducted in the UK with people who had either schizophrenia, schizoaffective disorder or bipolar disorder. The intervention was bespoke, and was compared to usual care.
- j. This has been rated as very serious, as the study had a drop-out rate of 30% (this information was taken from the individual study/publication), and was reported to have a high risk for masking of outcome assessment (this was taken from Table 2 in Peckham et al 2017).
- k. This has been rated as serious, as the total number of participants is low.
- l. Of these adverse events, 10 were classed as serious adverse events, of which all were deemed to be unlikely to be related or unrelated to the study by the authors of the systematic review (Peckham et al 2017). Of the 5 non-serious adverse events, 3 were deemed by the authors of the systematic review to be probably related to the study, and 2 unrelated.
- m. Of these adverse events, 2 were classed as serious adverse events, of which all were deemed to be unlikely to be related to the study by the authors of the systematic review (Peckham et al 2017). Of the 4 non-serious adverse events, 3 were deemed by the authors of the systematic review to be either definitely related or probably related to the study, and 1 unrelated.

CI: Confidence interval

Explanations

- a. Both Peckham et al (2017) and Tsoi et al (2013) identified the one same study for this. The study was conducted in the USA with people who had a diagnosis of schizophrenia or schizoaffective disorder. The intervention arms were as follows: 1. CR with money, 2. CR with money plus NRT, 3. care as usual. The information presented in the table is taken from Peckham et al (2017), as this paper is more recent, and the Tsoi et al (2013) paper only included a sub-sample of participants.
- b. This was rated as very serious, as Peckham et al 2017 (see Table 2) deemed the study to have high risk of bias for masking of outcome assessment and drop-out rates, and Tsoi et al 2013 deemed it to have an unclear risk for both these criteria (information taken from the 'characteristics of studies' tables).
- c. This has been rated as serious, as the total number of participants is low, and no effect sizes were provided.
- d. Funnel plots were not produced by the authors of the systematic review (Peckham et al 2017) due to the small number of studies, so publication bias was not detected.
- e. The information presented in the table is for the 'care as usual' group. The group with CR plus NRT resulted in the following effect size: 25/60 (41.7%). This information was taken from Table 3 in Peckham et al (2017).
- f. The information presented in the table is for the 'care as usual' group. The group with CR plus NRT resulted in the following effect size: 26/60 (43.3%). This information was taken from Table 3 in Peckham et al (2017).
- g. Both Peckham et al (2017) and Tsoi et al (2013) identified the one same study for this. The study was conducted in the US with people who had a diagnosis of schizophrenia or schizoaffective disorder. The intervention arms were as follows: 1. CR + bupropion, 2. CR + placebo, 3. bupropion, 4. placebo. The information presented in the table is taken from Tsoi et al (2013), as Peckham et al (2017) did not report on this outcome.
- h. This has been rated as very serious, as Peckham et al (2017) (see Table 2) rated drop-out as of high risk, and Tsoi et al (2013) rated both masking of outcome assessment and drop-out as of unclear risk of bias (this information was taken from the 'characteristics of included studies' tables).
- i. This has been rated as serious, as the total number of participants is very low, and no effect size was presented.

Additional evidence not mentioned in GRADE tables³

Smoking cessation advice for people with SMD

Khanna et al (2016) conducted a Cochrane review to assess the effects of smoking cessation advice for people with serious mental illness. The authors did not identify any RCTs that evaluated advice regarding smoking cessation for people with serious mental illness. The excluded studies illustrate that randomisation of packages of care relevant to smokers with serious mental illness is possible. Authors' conclusions: People with serious mental illness are more likely to smoke than the general population. Yet we could not find any high quality evidence to guide the smoking cessation advice healthcare professionals pass onto service users. This is an area where trials are possible and needed.

Further systematic reviews on tobacco cessation interventions for people with schizophrenia

Stubbs et al (2015) conducted a clinical overview to establish how smoking cessation should be promoted in practice. They found that a growing body of evidence supports pharmacological interventions to assist smoking cessation. The most promising evidence is for bupropion with several meta-analyses demonstrating its effectiveness. Currently, there is limited evidence demonstrating the effectiveness of nicotine replacement therapy (NRT) and varenicline, although this is likely to be due to the paucity of research. There are no consistent data to suggest that pharmacological interventions increase adverse events. Behavioural and psychosocial interventions also demonstrate promise, particularly when combined with pharmacotherapy. Careful monitoring of antipsychotic levels (in particular clozapine) is essential, and the promotion of physical activity may be useful to negate potential weight gain and diabetes risk following smoking cessation. Authors' conclusion: Evidence from systematic reviews and meta-analyses suggests that smoking cessation interventions are effective in people with schizophrenia, although more long-term research is required. Promoting smoking cessation should be given utmost priority in clinical practice, and we offer practical strategies to facilitate this.

Wu & Abughosh (2014) conducted a study to summarize the current evidence for efficacy of smoking cessation medications (nicotine replacement therapy, Bupropion SR, or Varenicline) as treatments for nicotine dependence in patients with schizophrenia. Seven original studies were included in this review (1 for NRT, 4 for Bupropion SR, and 2 for Varenicline). Majority of the medications achieved smoking cessation with a higher percentage as compared to placebo but most of the effects were not statistically significant. No significant changes in mental states were observed after the cessation treatments exposure. Authors' conclusions: Our review showed that most of the cessation medications slightly improved abstinence rates compared to placebo after 8 - 14 weeks of treatment, but this did not reach statistical significance. Only seven original studies were included due to limited available randomized controlled trials. Future studies could consider smoking reduction as an outcome as reaching abstinence might be difficult to achieve among schizophrenia patients.

Evins et al (2015) conducted a narrative review to present the evidence on safety and efficacy of smoking cessation interventions for those with serious mental illness. They recommended that smokers with schizophrenia spectrum disorders should receive varenicline or bupropion with or without nicotine replacement therapy in combination with behavioral treatment. Although more research is needed, preliminary evidence suggests that varenicline in combination with behavioral support is efficacious and well tolerated for smoking cessation for those with bipolar disorder and major depressive disorder. Controlled trials have found no evidence that in patients with serious mental illness, the use of pharmacotherapeutic cessation aids worsens psychiatric symptoms or increases the rate of psychiatric adverse events. Converging evidence indicates that a majority of smokers with serious mental illness want to quit smoking and that available pharmacotherapeutic cessation aids combined with behavioral support are both effective for, and well tolerated by, these smokers.

³ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

Further systematic reviews on tobacco cessation interventions for people with depression

van de Meer et al 2013 conducted a Cochrane review, to evaluate the effectiveness of smoking cessation interventions, with and without specific mood management components, in smokers with current or past depression. Forty-nine RCTs were included of which 33 trials investigated smoking cessation interventions with specific mood management components for depression. In smokers with current depression, meta-analysis showed a significant positive effect for adding psychosocial mood management to a standard smoking cessation intervention when compared with standard smoking cessation intervention alone (11 trials, N = 1844, RR 1.47, 95% CI 1.13 to 1.92). In smokers with past depression we found a similar effect (13 trials, N = 1496, RR 1.41, 95% CI 1.13 to 1.77). Meta-analysis resulted in a positive effect, although not significant, for adding bupropion compared with placebo in smokers with current depression (5 trials, N = 410, RR 1.37, 95% CI 0.83 to 2.27). There were not enough trial data to evaluate the effectiveness of fluoxetine and paroxetine for smokers with current depression. Bupropion (4 trials, N = 404, RR 2.04, 95% CI 1.31 to 3.18) might significantly increase long-term cessation among smokers with past depression when compared with placebo, but the evidence for bupropion is relatively weak due to the small number of studies and the post hoc subgroups for all the studies. There were not enough trial data to evaluate the effectiveness of fluoxetine, nortriptyline, paroxetine, selegiline, and sertraline in smokers with past depression. Twenty-three of the 49 trials investigated smoking cessation interventions without specific components for depression. There was heterogeneity between the trials which compared psychosocial interventions with standard smoking cessation counselling for both smokers with current and past depression. One trial compared nicotine replacement therapy (NRT) versus placebo in smokers with current depression and found a positive, although not significant, effect (N = 196, RR 2.64, 95% CI 0.93 to 7.45). Meta-analysis also found a positive, although not significant, effect for NRT versus placebo in smokers with past depression (3 trials, N = 432, RR 1.17, 95% CI 0.85 to 1.60). Three trials compared other pharmacotherapy versus placebo and six trials compared other interventions in smokers with current or past depression. The authors concluded that evidence suggests that adding a psychosocial mood management component to a standard smoking cessation intervention increases long-term cessation rates in smokers with both current and past depression when compared with the standard intervention alone. Pooled results from four trials suggest that use of bupropion may increase long-term cessation in smokers with past depression. There was no evidence found for the use of bupropion in smokers with current depression. There was not enough evidence to evaluate the effectiveness of the other antidepressants in smokers with current or past depression. There was also not enough evidence to evaluate the group of trials that investigated interventions without specific mood management components for depression, including NRT and psychosocial interventions.

Aldi et al (2018) conducted a systematic review of randomized clinical trials assessing the effectiveness of pharmacological, psychological or combined interventions for smoking cessation in subjects with current or past MDD/DS without medical or comorbid psychiatric disorder(s). Twenty-seven studies met the inclusion criteria. Nicotine, varenicline, Stage Care Intervention were more effective in smokers with current MDD; nicotine, fluoxetine plus nicotine were more effective in smokers with DS; nicotine plus fluoxetine or naltrexone were more effective in smokers with severe current DS. Cognitive Behavioural Therapy and Cognitive and Behavioural Cessation and relapse prevention skills training were superior to placebo in smokers with past MDD. The authors concluded that more research is needed into effectively addressing smoking in people with concurrent mental disorder. Data currently available are in need to be confirmed in randomized trials aimed at replicating the results and disentangling the effects of each therapeutic ingredient when a combination therapy is proposed. Studies on tolerability of treatments are warranted as well as those aimed at identifying factors of vulnerability to adverse effects. *Please note that this paper was given a low AMSTAR rating.*

Further systematic reviews on bupropion

Engelisch et al (2013) conducted a systematic review to evaluate the efficacy of bupropion on depression, negative symptoms, cognition, and smoking habits in schizophrenia and to appraise safety aspects. A total of 13 randomized controlled trials (28 publications), 3 open prospective evaluations, 5 multiple case reports, 22 single case reports, and 6 review articles were incorporated in the final analysis. They found that a total of 30 cases of bupropion-induced psychoses have been published, 17 (57%) of which were associated with the immediate-release drug formulation and 28 (93%) of which occurred without concomitant antipsychotic medication. In comparison, 229 schizophrenic patients on stable antipsychotic regimens were successfully treated with bupropion and experienced marked clinical improvement without developing psychosis. Pharmacokinetic interactions with antipsychotics were rare, whereas electroencephalographic abnormalities occurred frequently. Authors' conclusions: In schizophrenic patients treated with bupropion in addition to antipsychotics, the risk for bupropion-induced psychoses seems negligible. Further trials involving bupropion should integrate neurobiological methods and focus on negative symptoms and cognitive deficits in schizophrenia.

Further systematic reviews on varenicline

Kishi & Iwata (2015) updated Tsoi et al (2013) for varenicline adjuvant therapy for smoking cessation in people with schizophrenia. Seven studies (total $n = 439$), including 6 with only schizophrenia (total $n = 352$), 1 with both schizophrenia ($n = 77$) and bipolar disorder ($n = 10$), were included. Varenicline was not superior to placebo in smoking cessation ($RR = 0.79$, 95% CI 0.58-1.08, $p = 0.14$, 5 RCTs, $n = 322$). Varenicline failed to show its superiority to placebo for overall, positive, negative, and depressive symptoms. Moreover, there was no significant difference in the discontinuation rate due to all causes, clinical deterioration, or side effects between varenicline and placebo. Although varenicline caused less abnormal dreams/nightmares than placebo ($RR = 0.47$, 95% CI 0.22-0.99, $p = 0.05$, NNH = not significant, 4 RCTs, $n = 288$), it caused more nausea ($RR = 1.79$, 95% CI 1.20-2.67, $p = 0.004$, NNH = 6, $p = 0.004$, 6 RCTs, $n = 417$). We detected no significant difference in suicidal ideation and depression between varenicline and placebo. Our results suggest that although varenicline adjuvant therapy is well tolerated, varenicline is not superior to placebo for smoking cessation in people with schizophrenia. Because of the limited sample sizes of the available studies, future studies will require larger samples to ensure that these findings are generalizable.

Several systematic reviews assessed the adverse effects of varenicline in people with mental disorder:

1. Ahmed et al (2013) conducted a review of case reports, and identified 25 published cases. In most reports, patients had been admitted to psychiatric hospitals with serious neuropsychiatric adverse events (AEs) due to varenicline. The average patient age was 46.4 years, and 56% were men; 68% of patients had a psychiatric history. The onset of symptoms started 2 days to 3 months after the initiation of varenicline. One report described completed suicide in a man with no psychiatric history. In most cases (84%), the neuropsychiatric symptoms resolved after the discontinuation of varenicline. Analysis of all reports using the Naranjo causality scale, a method for estimating the probability of adverse drug reactions, indicated probable causality in 76% of the cases and definite causality in 12% of cases. The authors concluded that varenicline is associated with an increased risk of serious neuropsychiatric AEs, especially in patients with a psychiatric illness. They strongly recommended that varenicline be administered only to mentally stable patients and under close monitoring.
2. Hughes (2016) reviewed postmarketing analyses, case reports, clinical trials, uncontrolled observational studies, controlled observational studies, and studies in smokers with psychiatric problems that have tested the association of varenicline use with suicidal behaviors. Two pooled analyses of 10 and 17 placebo-controlled trials failed to find more suicidal outcomes in the varenicline condition. Seven large uncontrolled observational studies reported low rates of suicide outcomes in varenicline users ($<0.1\%$), and 1 study reported a higher rate (6%). Five large controlled observational studies did not find more suicide outcomes in varenicline users than in those using prescribed bupropion or over-the-counter nicotine medications. Small placebo-controlled trials and observational studies of smokers with current psychiatric problems did not find varenicline was associated with suicidal outcomes. Authors' conclusions: Among the more valid study designs (pooled analyses of placebo controlled trials or large

controlled observational studies), there is consistent evidence that varenicline either does not cause increased suicide outcomes, or if it does, the effect is very small. Warnings to consumers and clinicians should reflect, not just the results of postmarketing studies, but the results of the more valid research designs.

3. Rodrigues et al (2016) conducted a systematic review to assess evidence showing an association between the prescription of varenicline on psychiatric patients and induced worsening of psychiatric symptoms or de novo adverse symptomatology, particularly suicidal behaviour. Sixteen articles were found but only 5 studies were included, for matching inclusion criteria. We found four Randomized, Double-Blinded, Controlled Trials and one simple Randomized Trial. These articles included a total of 1457 patients. For mostly of these papers, trials, the main outcome was abstinence related, so the assessment of psychiatric side effects was mostly considered a secondary outcome. Only one article assessed varenicline safety and tolerability among psychiatric patients as a primary outcome. Main limitations founded on these studies were: number of patients included, a lack of differentiated groups with specific diagnosis, the way psychiatric adverse effects were assessed and funding. Authors' conclusions: More evidence is needed to assess an association between varenicline and suicidal behaviour and other psychiatric adverse effects. More trial involving different groups with a specific diagnosis would probably produce more specific outcomes. The effects of prescribed drugs, nicotine withdrawal effects and struggling with tobacco abstinence on worsening or inducing psychiatric symptoms is not clear.
4. Wu et al (2016) conducted a systematic review and meta-analysis of randomised controlled trials that compared varenicline with a placebo or an alternative intervention for smoking cessation or reduction for people with any type of severe mental illness. The systematic review included eight studies comprising 398 participants. The random-effect pooled estimates from the five studies that reported smoking-related outcomes found that varenicline is statistically superior to placebo in smoking cessation [risk ratios 4.33; 95% confidence interval (CI) = 1.96-9.56], and smoking reduction was higher in varenicline groups (mean reduced daily cigarettes was 6.39; 95% CI = 2.22-10.56). There was no significant difference regarding neuropsychiatric and other adverse events. The authors concluded that varenicline appears to be significantly more effective than placebo in assisting with smoking cessation and reduction in people with severe mental illness. There appears to be no clear evidence that varenicline was associated with an increased risk of neuropsychiatric or other adverse events compared with placebo.

Relevant guidelines

NICE guidelines Psychosis and schizophrenia in adults: prevention and management (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014):

- "Physical health": offer help to stop smoking; recognise possible impact of this on metabolism of other drugs (esp. clozapine and olanzapine).
- Consider: nicotine replacement therapy, bupropion, varenicline. Warn of side effects, monitor regularly.
- Re medication: discuss use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs, and possible interference with therapeutic effects of prescribed medication/psychological treatments.

NICE guidelines Bipolar disorder: assessment and management (Clinical guideline [CG185]; Published date: September 2014 Last updated: February 2016):

- Re medication: discuss use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs, and possible interference with therapeutic effects of prescribed medication/psychological treatments.

NICE guidelines Depression in adults with a chronic physical health problem: recognition and management (Clinical guideline [CG91]; Published date: October 2009):

- Recommendations to avoid excess eating, smoking, or alcohol, re: advice on sleep hygiene.

NICE guidelines Smoking: Acute, maternal and mental health services (Public Health guideline [PH48], November 2013):

Recommendation 3 Provide intensive support for people using acute and mental health services

Who should take action?

- Doctors, and stop smoking advisers, health and social care practitioners trained to provide intensive stop smoking support.

What action should they take?

- Discuss current and past smoking behaviour and develop a personal stop smoking plan as part of a review of their health and wellbeing.
- Provide information about the different types of stop smoking pharmacotherapies and how to use them.
- Provide information about the types of [intensive behavioural support](#) available.
- Offer and arrange or supply prescriptions of stop smoking pharmacotherapies (see [recommendation 6](#)).
- For anyone who does not want, is not ready or is unable to stop completely, encourage the use of licensed nicotine-containing products to help them abstain and provide intensive behavioural support to maintain abstinence from smoking while in secondary care. Follow recommendation 8 in NICE guidance on [tobacco: harm-reduction approaches to smoking](#) (NICE public health guidance 45) where appropriate.
- Offer, and if they agree, use measurements of exhaled carbon monoxide during each contact, to motivate and provide feedback on progress.
- Alert the person's healthcare providers and prescribers to changes in smoking behaviour because other drug doses may need adjusting (see [recommendation 7](#)).
- In addition, for people admitted to a secondary care setting:
 - Provide immediate support if necessary, and otherwise within 24 hours of admission.
 - Provide support (delivered in the setting) as often and for as long as needed during admission.
 - Offer weekly sessions, preferably face-to-face, for a minimum of 4 weeks after discharge. If it is not possible to provide this support after discharge, arrange a referral to a local stop smoking service.
- In addition, for people receiving secondary care services in the community or at outpatient clinics (including pre-operative assessments):
 - Provide immediate support in the outpatient setting.
 - Offer weekly sessions, preferably face-to-face, for a minimum of 4 weeks after the date they stopped smoking. Arrange a referral to a local stop smoking service, if preferred by the person.

Recommendation 6 Advise on and provide stop smoking pharmacotherapies

Who should take action?

- Stop smoking advisers and other healthcare practitioners who advise on, supply, or prescribe, pharmacotherapies.

What action should they take?

- Advise people who smoke that licensed nicotine-containing products and other stop smoking pharmacotherapies help people to stop smoking and reduce cravings.
- Emphasise that nicotine is not the major cause of damage to people's health from smoking tobacco, and that any risks from using licensed nicotine-containing products or other stop smoking pharmacotherapies are much lower than those of smoking.
- Recommend and offer:
 - licensed nicotine-containing products (usually a combination of transdermal patches with a fast-acting product such as an inhalator, gum, lozenges or spray) to all people who smoke^[5] **or**
 - varenicline^[6] or bupropion as sole therapy as appropriate. Do not offer varenicline or bupropion to pregnant or breastfeeding women or people under the age of 18. Varenicline and bupropion can be used with caution in people with mental health problems^[7].
- Encourage people who do not want (or do not feel able) to stop smoking completely (including pregnant or breastfeeding women) to use licensed nicotine-containing products to help reduce cravings to smoke during their stay or visit.
- If stop smoking pharmacotherapy is accepted, ensure that it is provided immediately.
- The person should remove [nicotine replacement therapy \(NRT\)](#) patches 24 hours before microvascular reconstructive surgery and surgery using vasopressin injections.
- When people are discharged from hospital ensure they have sufficient stop smoking pharmacotherapy to last at least 1 week or until their next contact with a stop smoking service.
- Encourage people who are already using an unlicensed [nicotine-containing product](#) (such as unlicensed electronic cigarettes) to switch to a licensed product^[8]. Advise the person of local policies on indoor and outdoor use of unlicensed nicotine-containing products.
- See also NICE guidance on [varenicline](#) (NICE technology appraisal guidance 123) and [smoking cessation services](#) (NICE public health guidance 10).

Cooper et al's (2016) BAP guidelines recommended the following:

- Tobacco smoking is an important additive risk factor for diabetes and CVD, and those who smoke should be referred to smoking cessation services

- Evidence suggests that all of the treatments below are most effective if delivered as part of an overall smoking cessation programme:
 - Use of nicotine replacement therapy (NRT) in smokers with psychosis is supported by open label studies
 - Individual RCTs of bupropion have small numbers of participants, and most do not demonstrate statistically significant effects, but meta-analysis of these support its use in psychosis.
 - Only one of three RCTs of varenicline demonstrates a statistically significant effect, but meta-analysis of these RCTs suggests a significant effect.

Kuipers et al's (2014) summary of updated NICE guidance recommended the following:

- Offer people with psychosis or schizophrenia who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential impact of reducing nicotine on the metabolism of other drugs, particularly clozapine and olanzapine. (New recommendation.) *[Based on the experience and opinion of the Guideline Development Group (GDG)]*
- Consider one of the following to help people stop smoking:
 - Nicotine replacement therapy (usually a combination of transdermal patches with a short acting product such as an inhalator, gum, lozenges, or spray) for people with psychosis or schizophrenia
 - Bupropion for people with a diagnosis of schizophrenia
 - Varenicline for people with psychosis or schizophrenia
 - *[Based on very low to moderate quality evidence from randomised controlled trials]*
 - Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first two to three weeks of treatment. (New recommendation.) *[Based on the experience and opinion of the GDG]*

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Bupropion has significant interactions with amitriptyline, fluoxetine, haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, and carbamazepine. With regards to anti-depressants: It is not recommended to combine bupropion with amitriptyline, as bupropion may elevate amitriptyline levels and thus, toxicity. If the two medications are used, monitor clinically for signs of amitriptyline toxicity or check amitriptyline levels

where available. Bupropion may also elevate fluoxetine levels; monitor patients on bupropion and fluoxetine for clinical signs of fluoxetine toxicity and/or serotonin syndrome. With regards to anti-psychotics: Bupropion is known to lower the seizure threshold, and as such, caution is advised when using bupropion with haloperidol, risperidone, chlorpromazine, fluphenazine, and clozapine, as these medicines are also associated with increased risk of seizures, and concurrent use may lower the seizure threshold further. Additional caution is advised for clozapine, as bupropion may increase clozapine levels. Patients should be monitored for signs of clozapine toxicity both in terms of clinical symptoms and by laboratory testing of levels. Clozapine doses may need to be adjusted accordingly, especially while starting, titrating, or stopping bupropion. With regards to mood-stabilizing medication: Carbamazepine may lower the levels (and efficacy) of bupropion. Doses of bupropion may need to be adjusted accordingly, with starting, titrating, or stopping carbamazepine.

There are no significant interactions between **nicotine-replacement therapy (NRT)** or **varenicline** and medicines used for SMD.

See Annex for further information.

WHO guidelines for general population

WHO's training package on Strengthening health systems for treating tobacco dependence in primary care (2013):

"The currently available effective tobacco cessation medications are: – nicotine replacement therapy (NRT): nicotine gum, nicotine patches, nicotine nasal spray, nicotine inhaler, nicotine lozenges/sublingual tablets; – non-nicotine medications: bupropion sustained release (SR), varenicline, cytisine, clonidine, triptiline.

According to USA clinical guidelines, NRT, bupropion and varenicline are first-line medications for treating tobacco dependence. Currently, NRT has the best balance of effectiveness, cost and safety. As a result, two forms of NRT (nicotine gum and nicotine patch) have been added to the WHO Model List of Essential Medicines."

See next page for relevant extracted tables from this document on bupropion, varenicline and NRT.

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Table 10. Description of NRT, Bupropion and varenicline

Medication	Who can use	Purpose of use	Advantages and disadvantages	General guidelines for use	Side-effects and warnings
Nicotine gum (OTC) Delivers nicotine through the lining of the mouth. Available dosage: 2mg, 4mg.	- Smokers 18 years and over. - Smokers with severe heart and circulation problems should start NRT under medical supervision. - Pregnant or breast-feeding women if they cannot stop without NRT.	- Withdrawal symptom relief. - Control of cravings/urges.	Pros - Convenient/flexible dosing. - Faster delivery of nicotine than the patches. Cons - May be inappropriate for people with dental problems and those with temporomandibular joint (TMJ) syndrome. - Should not eat or drink 15 minutes before use or during use. - Frequent use during the day is required to obtain adequate nicotine levels.	Dosing: Based on cigarettes/day (cpd) >20 cpd: 4 mg gum ≤20 cpd: 2 mg gum Based on time to first cigarette of the day: ≤30 minutes = 4 mg >30 minutes = 2 mg Initial dosing is 1–2 pieces every 1–2 hours (10–12 pieces/day). Taper as tolerated. Duration: up to 12 weeks with no more than 24 pieces to be used per day. How to use: It is not chewed like regular gum but rather is chewed briefly until you notice a "peppery" taste, then "parked" between cheek and gum for about 30 minutes.	- Hiccups - Jaw ache - Stomach irritation - Sore mouth
Nicotine patch (OTC) Delivers nicotine through skin. Available dosage: 24 hour delivery systems 7mg, 14mg, 21mg. 16 hour delivery systems 5mg, 10mg, 15mg.	The same as nicotine gum.	- Withdrawal symptom relief. - Control of cravings/urges.	Pros - Achieve high levels of replacement. - Easy to use. - Only needs to be applied once a day. Cons - Less flexible dosing. - Slow onset of delivery. - Mild skin rashes and irritation.	Dosing (24 hour patch): >40 cpd = 42 mg/day 21–39 cpd = 28–35 mg/day 10–20 cpd = 14–21 mg/day <10 cpd = 14 mg/day If a dose > 42mg/day may be indicated, contact the patient's prescriber. Adjust based on withdrawal symptoms, urges, and comfort. After 4 weeks of abstinence, taper every 2 weeks in 7–14 mg steps as tolerated. Duration: 8–12 weeks. How to use: Patches may be placed on any hairless area on the upper body, including arms and back. Rotate the patch site each time a new patch is applied to lessen skin irritation.	- Skin irritation - Allergy (not suitable if you have chronic skin conditions) - Vivid dreams and sleep disturbances

Medication	Who can use	Purpose of use	Advantages and disadvantages	General guidelines for use	Side-effects and warnings
Nicotine lozenge (OTC) Delivers nicotine through the lining of the mouth while the lozenge dissolves. Available dosage: 2 mg, 4 mg.	The same as nicotine gum.	- Withdrawal symptom relief. - Control of cravings/urges.	Pros - Easy to use. - Delivers doses of nicotine approximately 25% higher than nicotine gum. Cons - Should not eat or drink 15 minutes before use or during use.	Dosing: Based on time to first cigarette of the day: ≤30 minutes = 4 mg >30 minutes = 2 mg Based on cigarettes/day (cpd) >20 cpd: 4 mg ≤20 cpd: 2 mg Initial dosing is 1–2 lozenges every 1–2 hours (minimum of 9/day). Taper as tolerated. Duration: up to 12 weeks with no more than 20 lozenges to be used per day. How to use: The lozenge should be allowed to dissolve in the mouth. It should not be chewed or swallowed.	- Irritation of mouth - Irritation to stomach (nausea frequent 12–15%) - Hiccups - Heartburn
Nicotine nasal spray (Rx) Delivers nicotine through the lining of the nose when sprayed directly into each nostril. Available dosage: 0.5 mg nicotine in 50 µl aqueous nicotine solution.	The same as nicotine gum plus those who do not have - Underlying chronic nasal disorders - Severe reactive airway disease.	- Withdrawal symptom relief. - Control of cravings/urges.	Pros - Flexible dosing. - Can be used in response to stress or urges to smoke. - Fastest delivery of nicotine of currently available products but not as fast as cigarettes. Cons - Nose and eye irritation is common, but usually disappears within one week. - Frequent use during the day required to obtain adequate nicotine levels.	Dosing: 1 spray in each nostril, 1–2 times per hour (up to 5 times/hour or 40 times/day) Most average 14–15 doses/day initially Taper as tolerated. Duration: 3–6 months.	- Nasal irritation (runny nose, sneezing, burning sensation) - Coughing - Nausea - Headache - Dizziness - Irritated throat

Medication	Who can use	Purpose of use	Advantages and disadvantages	General guidelines for use	Side-effects and warnings
Nicotine inhaler (Rx) Delivers nicotine to the oral mucosa, not the lung, and enters the body much more slowly than the nicotine in cigarettes. Available dosage: 10 mg cartridge delivers 4mg inhaled nicotine vapour.	The same as nicotine gum plus those who do not have Bronchospastic disease.	- Withdrawal symptom relief. - Control of cravings/urges.	Pros - Flexible dosing. - Mimics the hand-to-mouth behaviour of smoking. - Few side effects. Cons - Frequent use during the day required to obtain adequate nicotine levels. - Should not eat or drink 15 minutes before use or during use.	Dosing: Minimum of 6 cartridges/day, up to 16/day Taper as tolerated (during the final 3 months of treatment). Duration: up to 6 months.	- Mouth or throat soreness or dryness - Coughing
Bupropion SR (Rx) Originally used as antidepressant. Affects the levels of neurotransmitters affecting the urge to smoke. Available dosage: 150 mg sustained release tablet.	All adult smokers except those - Pregnant or breast-feeding - Concomitant therapy with medications or medical conditions known to lower the seizure threshold - Severe hepatic cirrhosis.	- Withdrawal symptom relief (anxiety irritability and depression). - Abstinence.	Pros - Easy to use. - Pill form. - Few side effects. - May be used in combination with NRT. Cons - Contraindicated with certain medical conditions and medications.	Dosing: Take doses at least 8 hours apart. Start medication one week prior to the target quit date (TQD) 150 mg once daily for 3 days, then 150 mg twice daily for 4 days, then On TQD STOP SMOKING and continue at 150 mg twice daily for 12 weeks May stop abruptly; no need to taper.	- Dry mouth - Nervousness/difficulty concentrating - Rash - Headache, dizziness - Seizures (risk is 1/1,000) Warnings: advise patients to stop bupropion and contact a health-care provider immediately if they experience agitation, depressed mood, and any changes in behaviour that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behaviour.
Varenicline (Rx) Attaches to nicotinic receptors. Part blocking the reward effects of nicotine and part stimulating the nicotinic receptors. Available dosage: 0.5 mg, 1 mg tablet.	All adult smokers except those - Pregnant or breast-feeding - Severe renal impairment (dosage adjustment is necessary).	- Withdrawal symptom relief. - Control of cravings/urges. - Abstinence.	Pros - Easy to use. - Pill form. - Generally well tolerated. - No known drug interactions. Cons - Nausea is common.	Dosing: Take with food. Start medication one week prior to the TQD 0.5 mg once daily X 3 days, then 0.5 mg twice daily X 4 days, then On TQD STOP SMOKING AND take 1.0 mg twice daily for 11 weeks. May stop abruptly; no need to taper.	- Nausea - Sleep disturbances (insomnia, abnormal dreams) - Constipation - Flatulence - Vomiting Warnings: The same as for bupropion.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of findings table

	Outcome	Relative risk (RR) / Odds Ratio (OR) (confidence intervals) <i>values above 1 favour intervention unless otherwise specified</i>	Mean difference (MD) (confidence intervals) <i>negative values favour intervention</i>
GRADE Table 1 (Peckham et al 2017; Tsoi et al 2013; Roberts et al 2016) Bupropion vs. placebo	Tobacco cessation/abstinence rates – short term	RR 6.42 (0.82 to 50.07) VERY LOW	N/A
	Tobacco cessation/abstinence rates – medium term	RR 2.93 (1.61 to 5.34) LOW	N/A
	Tobacco cessation/abstinence rates – long term	RR 3.04 (1.10 to 8.42) VERY LOW	N/A
	Tobacco consumption rates – expired CO level (ppm) at end of treatment	N/A	MD 6.8 lower (10.79 lower to 2.81 lower) VERY LOW
	Tobacco consumption rates – expired CO level (ppm) at 6-month follow-up	N/A	MD 5.55 lower (17.89 lower to 6.78 higher) VERY LOW
	Tobacco consumption rates – change in number of CPD at end of treatment (abstinence studies)	N/A	MD 10.77 lower (16.52 lower to 5.01 lower) VERY LOW
	Tobacco consumption rates – change in number of CPD at 6-month follow-up (abstinence studies)	N/A	MD 0.4 higher (5.72 lower to 6.53 higher) VERY LOW
	Tobacco consumption rates – change in number of CPD at end of treatment (reduction studies)	N/A	MD 2.61 lower (7.99 lower to 2.77 higher) VERY LOW

	Respiratory disease outcomes (COPD, asthma)	N/A	
	Frequency of adverse events / side-effects	OR 0.93 (0.18 to 4.74) VERY LOW <i>values below 1 favour intervention</i>	N/A
GRADE Table 2 (Peckham et al 2017; Tsoi et al 2013 ; Roberts et al 2016) Varenicline vs. placebo	Tobacco cessation/abstinence rates	RR 4.13 (1.36 to 12.53) LOW	N/A
	Tobacco consumption rates	Narrative Significant effect in favour of intervention in short-term. VERY LOW	
	Respiratory disease outcomes (COPD, asthma)	N/A	
	Frequency of adverse events / side-effects	OR 1.29 (0.47 to 3.56) VERY LOW <i>values below 1 favour intervention</i>	N/A
GRADE Table 3 (Secades-Villa et al 2017; Tsoi et al 2013) Nicotine replacement therapy (NRT) vs. placebo	Tobacco cessation/abstinence rates	RR 1.56 (0.94 to 2.57) VERY LOW	N/A
	Tobacco consumption rates	Narrative Inconsistent results, though some beneficial significant effects in favour of NRT. VERY LOW	
	Respiratory disease outcomes (COPD, asthma)	N/A	
	Frequency of adverse events / side-effects	N/A	
GRADE Table 4 (Peckham et al 2017) Specialised smoking	Tobacco cessation/abstinence rates – median 6 months	RR 1.32 (0.85 to 2.06) VERY LOW	N/A

cessation interventions vs. standard smoking cessation interventions	Tobacco cessation/abstinence rates – median 12 months	RR 1.33 (0.85 to 2.08) VERY LOW	N/A
	Tobacco consumption rates	N/A	
	Respiratory disease outcomes (COPD, asthma)	N/A	
	Frequency of adverse events / side-effects	32.6% intervention vs. 11.8% controls VERY LOW	
GRADE Table 5 (Peckham et al 2017 ; Tsoi et al 2013) Contingent reinforcement vs. care as usual	Tobacco cessation/abstinence rates – 5 month follow-up	38.3% intervention vs. 5.0% controls VERY LOW	
	Tobacco cessation/abstinence rates – 8.5 month follow-up	36.7% intervention vs. 8.3% controls VERY LOW	
	Tobacco consumption rates	Narrative Significant effect in favour of intervention. VERY LOW	
	Respiratory disease outcomes (COPD, asthma)	N/A	
	Frequency of adverse events / side-effects	N/A	

Evidence to Decision Table

	JUDGEMENT ⁴	EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	People with SMD are twice as likely to smoke as the general population (around 61% of people with SMD smoke compared to 33% in the general population), they smoke more on average, and are less likely to quit smoking (CDC 2015). Tobacco use has been identified as a leading preventable cause of premature mortality in people with SMD as well as the general population and is an population. People with SMD have been reported to die 15-20 years earlier on average than people in the general population and this is often due to preventable smoking-related health conditions (Trainor & Leavey 2017), for example due to heart disease, cancer and lung disease, which can all be caused by smoking.	Comprehensive tobacco control at the policy level is of paramount public health focus
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	In regards to the desirable anticipated effects, the level of evidence varies for the different interventions included in this review: • Bupropion: There was a some evidence of an effect on tobacco cessation/abstinence rates in favour of bupropion. There was also some evidence of an effect in favour of bupropion on most of the outcomes related to tobacco consumption rates (apart from for change in number of CPD at 6-month follow-up). • Varenicline: There were some evidence in favour of varenicline both for tobacco cessation/abstinence rates and tobacco consumption rates (though for the latter possibly less so in the long-term). • Nicotine replacement therapy (NRT): At present, there is insufficient evidence to conclude on NRT on tobacco cessation/abstinence rates in people with SMD in the current review. .	Interventions are known to be effective in the general population with respect to smoking cessation

⁴ These were made based on the available evidence and/or the GDG's expertise.

		- Specialised smoking cessation interventions: There was a small effect in favour of the interventions for tobacco cessation/abstinence rates, but this was not statistically significant. There was no evidence available for tobacco consumption rates. - Contingent reinforcement: There was some evidence in favour of this intervention for both tobacco cessation/abstinence rates and tobacco consumption rates, though statistical significance was not assessed for the former. - There was no evidence available for respiratory disease outcomes for any of the interventions.	
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? - Large - Moderate X Small - Trivial - Varies - Don't know	In regards to undesirable anticipated effects, these also varied for the different interventions: - Bupropion: There was a very small effect in favour of bupropion for frequency of adverse events / side-effects, though this was not statistically significant. However, significant drug-drug interactions have been reported for several anti-psychotics, anti-depressants, and mood-stabilizing medications. - Varenicline: There was a small effect in favour of placebo compared to varenicline for frequency of adverse events / side-effects, though this was not statistically significant. Evidence on this from other additional studies is also inconclusive; whilst some studies have reported increased adverse events for varenicline (Ahmed et al 2013), other studies have not found any significant adverse effects (Hughes 2016; Wu et al 2016) or relatively minor adverse events such as nausea (Kishi & Iwata 2015), and yet others have been inconclusive (Rodrigues et al 2016). - The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) study found that that both varenicline and bupropion did not significantly increase the risk of neuropsychiatric adverse events (including anxiety, depression, aggression, psychosis, and suicidal behaviour) when compared with placebo or nicotine patch in patients with or without a history of psychiatric disorders (Anthenelli 2016) - NRT: No detailed is evidence available, although one study (Dalak 1999) reported no evidence of nicotine toxicity or significant side-	Risk of overdose in Bupropion and risk of worsening psychosis and mania. People taking Bupropion, Varenicline may have increased risk of neuropsychiatric symptoms, monitor first 2-3 weeks. Possibility of drug interactions between these medicines and psychotropic medicines

		effects for NRT compared to placebo, but more abnormal involuntary movement for people with NRT. • Specialised smoking interventions: A higher number of adverse effects were found for the intervention compared to standard smoking interventions, though the authors considered it unlikely that these were due to the study intervention. • Contingent reinforcement: No evidence available.	
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? Very low X ○ Low ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence of effects was rated to be very low for all interventions, with a few exceptions: • Bupropion: Evidence for tobacco cessation/abstinence rates in the medium term were rated as of low quality. • Varenicline: Evidence for tobacco cessation/abstinence rates were rated as of low quality. • All other certainty of the evidence of effects were rated to be of very low quality.	Refer to general population data
VALUES AND PREFERENCES	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability X Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	<i>Attitudes of people with mental health problems about tobacco use and facilitators and/or barriers to cessation</i> Systematic reviews and primary research studies have found several self-reported barriers to tobacco cessation by people with mental health problems, including smoking for stress management / coping resource, relaxation, lack of support from health and other service providers, the high prevalence and acceptability of smoking, low levels of motivation, concerns about ability of cessation services to handle mental health issues, identity and belonging / existential purposes, social inclusion, relief from boredom, that they would have to give up something they found pleasurable, and symptom / mental health management (Kerr et al 2013; Peckham et al 2016; Trainor & Leavey 2017; Twyman et al 2014).	

	Conversely, facilitators and reasons to stop using tobacco that have been reported by people with mental health problems include cost savings and health benefits (Kerr et al 2013; Peckham et al 2016; Trainor & Leavey 2017). Overall, self-reported barriers appear to outweigh facilitators / reasons to stop using tobacco for people with mental health problems (Kerr et al 2013), with smoking being considered the social norm and being embedded in the culture of mental health settings (Kerr et al 2013; Trainor & Leavey 2017). This is despite the finding that no published evidence is available to support the hypothesis that quitting smoking is harmful to the mental health of people with schizophrenia, nor that smoking cessation placed smokers with a history of major depression at increased risk of worsening symptoms nor relapse, and may even improve their mood (Ragg et al 2013). Siru et al (2009) found that people with mental health disorders overall are as motivated to quit smoking as the general population, although those with psychotic disorders may be less motivated than individuals with depression. The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012). <i>Attitudes of mental health professionals</i> Sheals et al (2016) found in a systematic review that included 38 studies including 16,369 participants that 42.2% (95%CI 35.7-48.8) of mental health professionals reported perceived barriers to smoking cessation interventions, 40.5% (95%CI 30.4-51.0) negative attitudes towards smoking cessation and 45.0% (95%CI 31.9-58.4) permissive attitudes towards smoking. The most commonly held beliefs were that patients are not interested in quitting (51.4%, 95%CI 33.4-69.2) and that quitting smoking is too much for patients to take on (38%, 95%CI 16.4-62.6). Qualitative findings were consistent with quantitative results, revealing a	
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		culture of smoking as "the norm" and a perception of cigarettes as a useful tool for patients and staff. Kerr et al (2013) also reported that professionals often failed to raise the issue of smoking/cessation as they believed it would damage their relationship with clients. <i>Attitudes of family members</i> An online study of 256 family members found that one-quarter of respondents agreed that people with mental illness must smoke to manage mental health symptoms, nearly half (48%) expressed uncertainty about whether nicotine replacement therapy is harmful for this population, and 69% believed that family members do not have the skills to help an individual with mental illness quit smoking (Ashbrenner et al 2017).	
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The balance between desirable and undesirable effects varied for the different interventions: • Bupropion: Evidence collected from the systematic reviews suggests a balance towards desirable effects in favour of bupropion; however, significant drug-drug interactions have been reported for several anti-psychotics, anti-depressants, and mood-stabilizing medications, which may counter the balance between desirable and undesirable effects. • Varenicline: Evidence suggests a balance towards desirable effects in favour of varenicline, though there is the possibility (though uncertain) of undesirable adverse events. • NRT: The balance between desirable and undesirable effects is unclear, as no high-quality data were available on undesirable effects. • Specialized smoking cessation interventions: The balance between desirable and undesirable effects is unclear. • Contingent reinforcement: The balance between desirable and	

		undesirable effects is unclear, as there were no data available on undesirable effects, though the intervention does appear to produce favourable outcomes.	
RESOURCES REQUIRED	How large are the resource requirements (costs)? ○ Large costs X ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Peckham et al (2015) conducted a pilot trial for a bespoke individually-tailored smoking cessation (BSC) intervention for people with SMD (which included pharmacotherapy such as bupropion, varenicline and NRT, as well as non-pharmacological interventions), and estimated the incremental cost of providing the BSC intervention over and above usual care to be £221 (SD £160) per participant. When the wider use of health-care and social care and prescriptions was included, the total cost in the BSC group was £12,674 (SD £16,596) per participant, compared with £6867 (SD £6026) per participant in the usual-care group. However, because of the small sample size, the authors recommended that these results should be treated with caution as the means are influenced by extreme values. Combining costs with the number of successful quitters at 12 months, the incremental cost was £58,197 per quitter. However, these results are from a pilot trial which was not powered to detect a significant difference from an economic perspective. It is also likely that in the longer term, beyond the 12-month follow-up, cost savings may accrue as a result of successful quits. Furthermore, improvements in health-related quality of life would be expected beyond the trial follow-up. In terms of clinical effectiveness of the intervention, at 12 months the chances of participants having quit smoking were three times higher in the intervention group. Of the pharmacological interventions included in this review, the following are included in the essential medicines list (EML):	

		• Bupropion: Not included in EML. • Varenicline: Not included in EML. • NRT: Included in EML. According to the WHO training package on the treatment of tobacco dependence in primary care, NRT, bupropion and varenicline are first-line medications for treating tobacco dependence, and NRT currently has the best balance of effectiveness, cost and safety. As a result, two forms of NRT (nicotine gum and nicotine patch) have been added to the WHO Model List of Essential Medicines. The resource requirements for the pharmacological interventions is likely to be lower than for the non-pharmacological interventions (due to the elevated training and human resource costs associated with non-pharmacological interventions), though of the included pharmacological interventions only NRT is included in the essential medicines list.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ X Low ○ Moderate ○ High ○ No included studies	See above.	

COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ X No included studies	A systematic review by Park et al (2013) on the cost-effectiveness of health promotion interventions for people with mental health problems found one relevant study and estimated that there was a 74% chance that a stepped smoking cessation intervention was cost-effective for people with depression (the intervention involved three computer-mediated assessments of readiness to quit smoking, six psychological counselling sessions, up to ten weeks nicotine replacement therapy, and offer of sustained-release bupropion and two additional counselling sessions). According to the WHO training package on the treatment of tobacco dependence in primary care, currently NRT has the best balance of effectiveness, cost and safety of medications to treat tobacco dependence.	
EQUITY	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ X Increased ○ Varies ○ Don't know	Since people with SMD are twice as likely to smoke as the general population, smoke more on average, and are less likely to quit smoking (CDC 2015), the interventions would likely improve equity in health, as they would address the heightened risk of tobacco use and its associated premature mortality amongst people with SMD compared to the general population. CDC's <i>Best Practices User Guide: Health Equity in Tobacco Prevention and Control</i> (2015) included people with mental health disorders as one of the priority populations for whom inequity should be aimed to be reduced. Studies have shown that untargeted tobacco use cessation interventions may result in increased inequality in tobacco use. For example, a systematic review that looked at the equity impact of European individual-level smoking cessation interventions to reduce smoking in adults found that although tobacco use interventions had contributed to reducing adult	

		smoking overall, this was less the case for people from lower socioeconomic (SES) groups, thereby increasing inequalities in smoking. Smoking services targeting lower-SES groups (specifically through the UK NHS services) appeared to reduce inequalities in smoking through increased relative reach (Brown et al 2014), providing support for targeted tobacco use cessation interventions.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ X Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence was identified for this. High drop-out rates were common in many of the included studies, though this could be due to the barriers associated with tobacco cessation outcomes amongst people with SMD, mental health professionals or family members (see above), or problems with the studies, rather than the individual interventions.	
FEASIBILITY	Is the intervention feasible to implement? ○ No ○ Probably no ○ X Probably yes ○ Yes ○ Varies ○ Don't know	Most studies have been conducted in high-income countries, with the following exceptions: • Bupropion: China, Iran (as well as USA) • Varenicline: USA and Canada only • NRT: USA only • Specialised smoking cessation interventions: USA, Australia, UK only • Contingent reinforcement: USA only Only NRT was included in the essential medicines list.	

		For the non-pharmacological interventions, although intervention features, such as duration or frequency, could possibly be adapted for each particular setting, e.g. by being administered by suitably trained and supported non-specialists, there is no direct evidence available to support this.	
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WHO guidelines for general population

In the general population, WHO recommends either bupropion, varenicline or NRT for the treatment of tobacco cessation, though NRT is considered to have the best balance of effectiveness, cost and safety, and has therefore been included in the essential medicines list (whereas bupropion and varenicline have not been included).

GDG Recommendations

For people with severe mental disorder (SMD) who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

TYPE OF RECOMMENDATION	Strong recommendation against the option ○	Conditional recommendation against the option ○	Conditional recommendation for either the option or the comparison ○	Conditional recommendation for the option X	Strong recommendation for the option ○
RECOMMENDATION	Recommendation: In the context of tobacco cessation programmes: Recommendation 1: In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (<i>Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package</i>) (http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/). (<i>Strength of recommendation: conditional; quality of evidence: Very low</i>). Recommendation 2: In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population. (<i>Strength of recommendation: conditional; quality of evidence: Very low</i>). Recommendation 3. In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco smoking cessation. (<i>Strength of recommendation: conditional; quality of evidence: Very low</i>). <u>Additional considerations</u>				

	• Tobacco cessation interventions should be considered as part of broader implementation packages as described in <i>WHO's MPOWER</i> (WHO., 2008) package of effective tobacco control measures to: Monitor tobacco use and prevention policies; Protect people from tobacco smoke; Offer help to quit tobacco use; Warn about the dangers of tobacco through pack warning labels and anti-tobacco mass media campaigns; Enforce bans on tobacco advertising, promotion and sponsorship; and Raise taxes on tobacco. • The behavioral intervention programme can build on the WHO training package and should be tailored to the needs of the population. This is based on the principles of motivational interviewing and aims to increase the person's intrinsic motivation for change based on the person's own personal goals and values. • Choice of pharmacotherapy will be understandably influenced by resource availability. In people with SMD, varenicline seems to have the highest efficacy, followed by bupropion with or without nicotine replacement therapy, followed by nicotine replacement therapy (nicotine patch) alone. • Prescribers should take into account potential interactions between bupropion, varenicline with psychotropic medications as well as possible contra-indications. • Smoking cessation can cause an increase in serum levels of anti-psychotic medication, and that smoking cessation needs to be accompanied by a reduction in dose to avoid toxicity. Smoking cessation programmes therefore need to be accompanied by monitoring of clinical state, and where appropriate monitoring of serum levels. •
JUSTIFICATION	Behavioural treatment alone for tobacco smoking cessation has a low abstinence rate in SMD of about 4 percent which is why combination behavioural treatment and pharmacotherapy is recommended for the population with SMD. Varenicline's efficacy has been shown to be the highest of the pharmacotherapy choices for persons with SMD including when compared to bupropion(Anthenelli <i>et al.</i>, 2016). Evidence for efficacy of bupropion comes from several studies included in the Cochrane review such as the EAGLES trial (Tsoi, 2013), Evidence for efficacy of nicotine patch vs. placebo can be seen in the EAGLES trial. At present there is insufficient evidence to indicate whether specialised smoking cessation interventions (vs. standard smoking cessation) and contingent reinforcement (vs. care as usual) are beneficial for the cessation of smoking in people with SMD. While there are no known interactions between NRT or varenicline and medicines used for SMD, there are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction. There is some evidence that people taking bupropion, and varenicline may have increased risk

	of neuropsychiatric symptoms. Although the evidence specifically for people with SMD is limited with few studies of small size, WHO has comprehensive tools for tobacco cessation in the general population and the GDG agreed based on their expert judgment that there was no suggestion of inconsistency with the evidence for tobacco cessation interventions in the general population and in people with SMD. The GDG agreed that the benefits of the interventions outweighed the harms while recognising that prescribers should take into account potential interactions between bupropion with psychotropic medications as well as possible contra-indications of the use of bupropion and varenicline in people with SMD. In view of the low quality evidence, the GDG used conditional recommendations for tobacco cessation interventions in people with SMD.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	1. More intervention studies are needed in SMD populations and tobacco cessation

Remarks

- Almost all of the evidence comes from high-income countries.

1. WHO training package on Strengthening health systems for treating tobacco dependence in primary care (2013)
2. Taylor et al. The Maudsley Prescribing Guidelines (2018) *In press*

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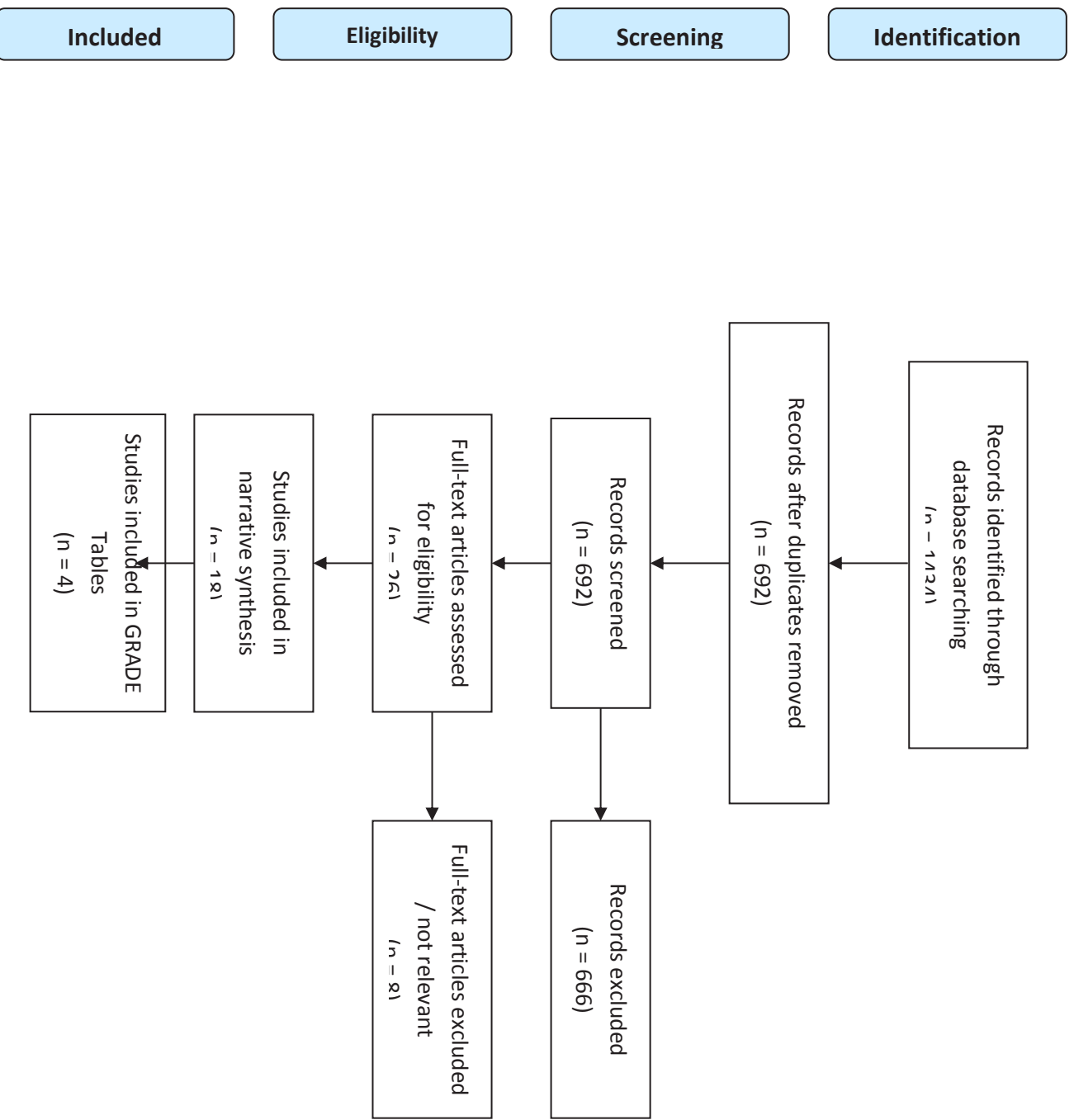
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**PRISMA Flow Diagram for systematic review of the reviews:
SMD and tobacco cessation**



EVIDENCE PROFILE

WEIGHT MANAGEMENT

PICO QUESTIONS:

3.1 For people with severe mental disorder (SMD) who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

3.2 For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Background on the PICO question

The majority of deaths amongst people with SMD are attributable to physical diseases. People with SMD are also more likely to engage in lifestyle behaviours, which increase the risk of developing physical illnesses.

Persons with SMD are 50% more likely to be obese (Compton et al., 2006). Among persons with SMD, 50% of women and 41% of men were obese compared with 27% and 20% respectively in the demographically matched comparison group (Dickerson et al., 2006); a higher BMI was associated with current hypertension and diabetes, a wish to weigh less and reduced health-related functioning (Dickerson et al., 2006). Similar results from the United Kingdom (UK) show rates of obesity to be about 50.6% among women and 28.7% of men between the ages of 18 to 44 years were obese compared with 16.6% and 13.6% in the general population respectively (Filik et al., 2006). Another study found over a third (35.0%) of persons with SMD were obese (BMI>30), while 19.4% were morbidly obese (BMI>40) (Filik et al., 2006). Among 57 studies summarizing the prevalence of different conditions in those with SMD, the median overweight prevalence was 29.0% (range: 25.0-58.0%) and the median obesity prevalence was 40.6% (range: 26.0-55.0%) (Janssen et al., 2015) and this was somewhat higher for those dwelling in the community versus inpatients, whereas in the US adult population the prevalence rate ranges from 33.1%-35.4% for overweight and 29.4%-35.7% for obesity depending on the measurement method used (Janssen et al., 2015).

Persons with SMD commonly have poor diets (Henderson et al., 2006). They consume more sugar and saturated fats than the general population (Dipasquale, et al., 2013), are less likely to exercise (Daumit et al., 2005), and spend over 12 hours in sedentary activities on a daily basis (Janney et al., 2013). This is also true in non-Western countries, such as Korea, where there is a high prevalence of metabolic syndrome, including abdominal

obesity and dyslipidemia, which might be related to a combination of adverse side effects of antipsychotic medication and physical inactivity (Kim, 2010). For more information regarding the differential side effect profiles of antipsychotic medications, specifically with regards to second-generation antipsychotic medications and weight gain, please refer to the mhGAP Evidence Resource Center recommendations on this topic¹. Stubbs et al (2017) reported that prevalence of low physical activity was 39.2% (95%CI = 37.0%–41.2%) amongst people with psychosis, which varied according to male sex (odds ratio (OR) = 1.33), increasing age, unemployment (vs. employed OR = 2.50), urban setting (vs. rural OR = 1.75), inadequate fruit consumption (vs. adequate fruit intake OR = 3.03), depression (OR = 1.33), sleep/energy disturbance, and mobility limitations, which were significantly associated with low physical activity. Marital status, education, wealth, smoking, vegetable and alcohol consumption, anxiety, cognition, pain, and chronic medical conditions were not significant correlates.

This document covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD who are overweight or obese, or who are at risk of becoming overweight or obese. Those outcomes were included, which were considered to be critical or important to this population group.

¹ Tarsitani L, Barbui C. Second-generation antipsychotic medications for psychotic disorders (including schizophrenia). mhGAP Evidence Resource Center. World Health Organization. Geneva, 2015 DOI:10.1016/S0140-6736(13)60733-3.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Being overweight or obese

Population: People with SMD who are overweight or obese

Intervention:

- non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:
 - Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
 - Pharmacological interventions: weight-loss medication (e.g. orlistat)
 - Pharmacological management strategies: e.g. switching antipsychotic medication

Comparison: care as usual and/or placebo

Outcomes:

- Critical
 - Change in weight
 - Mean BMI (kg/m²) or change in BMI
- Important:
 - Maintenance of weight change/attenuation/prevention of weight gain
 - Reduced sedentary behaviour
 - Frequency of adverse events/side-effects

At risk of becoming overweight or obese

Population: people with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

Intervention: non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

Comparison: care as usual

Outcomes:

- Critical
 - Change in weight
 - Mean BMI (kg/m²) or change in BMI
 - Maintenance of weight change
 - Attenuation/prevention of weight gain
- Important:
 - Reduced sedentary behavior
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process***INCLUDED IN GRADE TABLES***

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Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

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PICO Table

People with SMD who are overweight or obese

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Metformin vs. placebo	Change in weight	De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341 Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome. Complementary systematic review (meta-analysis) used, as it reports on percentage of clinically relevant weight loss as 'change in weight' outcome for people with SMD.
		Mean BMI (kg/m ²) or change in BMI	De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Maintenance of weight change / attenuation / prevention of weight gain	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis.	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this

			Schizophr Bull. 2014; 40(6): 1385-1403	outcome.
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
2	Amantadine vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
3	Aripiprazole vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia:	Most recent high-quality comprehensive systematic review (meta-analysis) for

			a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
4	Fluoxetine vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Reduced sedentary	No relevant systematic review available.	N/A

		behaviour		
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
5	Nizatidine vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
6	Orlistat vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary	No relevant systematic review available.	N/A

		behaviour		
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
7	Reboxetine vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
8	Rosiglitazone vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A

		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
9	Sibutramine vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
10	Topiramate vs. placebo	Change in weight	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
11	Anti-psychotic switching from olanzapine vs.	Change in weight	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With	Most recent high-quality comprehensive systematic

	olanzapine		Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	No relevant systematic review available.	N/A
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
12	Short-term lifestyle interventions (6 months and under) vs. care as usual	Change in weight	Naslund JA et al. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: A systematic review and meta-analysis. General Hospital Psychiatry. 2017; 47: 83-102	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD.
		Mean BMI (kg/m2) or change in BMI		
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD that reported on adverse events / side-effects (Naslund et al 2017 did not include this

				outcome).
13	Long-term lifestyle interventions (12 months and over) vs. care as usual	Change in weight	Naslund JA et al. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: A systematic review and meta-analysis. General Hospital Psychiatry. 2017; 47: 83-102	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m2) or change in BMI	Naslund JA et al. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: A systematic review and meta-analysis. General Hospital Psychiatry. 2017; 47: 83-102	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Maintenance of weight change / attenuation / prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behaviour	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A

People with SMD who are at risk of becoming overweight or obese

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
14	Lifestyle interventions vs care as usual	Change in weight	Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Mean BMI (kg/m ²) or change in BMI	Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18	Most recent high-quality comprehensive systematic review (meta-analysis) for people with SMD for this outcome.
		Maintenance of weight change	No relevant systematic review available.	N/A
		Attenuation/prevention of weight gain	No relevant systematic review available.	N/A
		Reduced sedentary behavior	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A

Narrative description of the studies that went into analysis²

De Silva et al (2016) conducted a systematic review to assess the efficacy of metformin in the treatment of antipsychotic induced weight gain. Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE were searched for the period January 2000-December 2015. Meta-analysis was carried out using the random effects model. Meta-analysis of 12 published studies with a total of 743 patients found that in patients treated with antipsychotics, metformin treatment resulted in significantly better anthropometric and metabolic parameters than placebo. The mean change in weight was -3.27 kg (95 % CI -4.66 to -1.89) ($Z = 4.64$, $p < 0.001$). Metformin compared to placebo resulted in significant reduction in BMI [-1.13 kg/m² (95 % CI -1.61 to -0.66)] and insulin resistance index [-1.49 (95 % CI -2.40 to -0.59)] but not fasting blood sugar [-2.48 mg/dl (95 % CI -5.54 to 0.57)]. Authors' conclusion: This meta-analysis confirms that metformin is effective in treating antipsychotic induced weight gain in patients with schizophrenia or schizoaffective disorder.

Gierisch et al (2013, 2014) conducted a systematic review to evaluate interventions to improve CVD risk factors in adults with SMD. Of 35 eligible studies, most enrolled patients with schizophrenia who were prescribed antipsychotics. Most studies were designed to control weight ($n=28$); one study specifically addressed diabetes management, none targeted hyperlipidemia, and three were multicondition interventions. Most studies were efficacy trials comparing behavioral interventions with control; none evaluated peer and family support. There were few direct comparisons of active interventions; effects on overall CVD risk, physical functioning, or cardiovascular events were reported rarely. Compared with controls, behavioral interventions (mean difference [MD] -3.13 kg; 95% CI, -4.21 to -2.05), metformin (MD -4.13 kg; CI, -6.58 to -1.68), the anticonvulsive medications topiramate and zonisamide (MD -5.11kg; CI, -9.48 to -0.74), and adjunctive or antipsychotic switching to aripiprazole improved weight control. However, aripiprazole switching may be associated with higher rates of treatment failure. Nizatidine did not improve any outcome. The evidence was insufficient for all other interventions and effects on glucose and lipid control. Authors' conclusions: Few studies have evaluated interventions to address one or more CVD risk factors in patients with SMD. Comparative effectiveness studies are needed to test multimodal strategies, agents known to be effective in non-SMI populations, and antipsychotic-management strategies.

Mizuno et al (2014) conducted a systematic review to determine the effectiveness of medications to counteract antipsychotic-induced metabolic adversities in patients with schizophrenia. Forty trials representing 19 unique interventions were included in this meta-analysis. Metformin was the most extensively studied drug in regard to body weight, the mean difference amounting to -3.17 kg (95% CI: -4.44 to -1.90 kg) compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also different from placebo. Furthermore, metformin and rosiglitazone improved insulin resistance, while aripiprazole, metformin, and sibutramine decreased blood lipids. Authors' conclusions: When nonpharmacological strategies alone are insufficient, and switching antipsychotics to relatively weight-neutral agents is not feasible, the literature supports the use of concomitant

² Please note that this section includes the abstracts as taken directly from the publications.

metformin as first choice among pharmacological interventions to counteract antipsychotic-induced weight gain and other metabolic adversities in schizophrenia.

Naslund et al (2017) conducted a systematic review and meta-analysis to estimate effects of lifestyle intervention participation on weight reduction among overweight and obese adults with serious mental illness. Seventeen studies met inclusion criteria (1968 participants; 50% male; 66% schizophrenia spectrum disorders). Studies were grouped by intervention duration (≤ 6 -months or ≥ 12 -months). Lifestyle interventions of ≤ 6 -months duration showed greater weight reduction compared with controls as indicated by effect size for weight change from baseline (SMD = - 0.20; 95% CI = - 0.34, - 0.05; 10 studies), but high statistical heterogeneity ($I^2 = 90\%$). Lifestyle interventions of ≥ 12 -months duration also showed greater weight reduction compared with controls (SMD = - 0.24; 95% CI = - 0.36, - 0.12; 6 studies) with low statistical heterogeneity ($I^2 = 0\%$). Authors' conclusion: Lifestyle interventions appear effective for treating overweight and obesity among people with serious mental illness. Interventions of ≥ 12 -months duration compared to ≤ 6 -months duration appear to achieve more consistent outcomes, though effect sizes are similar for both shorter and longer duration interventions.

Teasdale et al (2017) subjected randomised controlled trials of nutrition interventions in people with SMD to systematic review and meta-analysis. Interventions led to significant weight loss (19 studies), reduced body mass index (17 studies), decreased waist circumference (10 studies) and lower blood glucose levels (5 studies). Dietitian-led interventions (6 studies) and studies delivered at antipsychotic initiation (4 studies) had larger effect sizes. Authors' conclusions: Evidence supports nutrition interventions as standard care in preventing and treating weight gain among people experiencing SMD.

GRADE Evidence Tables (being overweight or obese)³

Table 1: Metformin vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Metformin compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography:

De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours metformin)												

³ See Annex 5, page **XX** for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
10 ^a	randomised trials	serious ^b	serious ^c	not serious	not serious	None detected ^d	340	341	-	MD 3.24 lower (4.72 lower to 1.76 lower) ^e	⊕⊕○○ LOW	CRITICAL
Change in weight - percentage of clinically relevant weight loss (OR above 1 favours intervention) ^f												
4 ^g	randomised trials	serious ^h	very serious ⁱ	not serious	not serious	publication bias strongly suspected ^j	46/177 (26.0%)	11/174 (6.3%)	OR 5.89 (1.81 to 19.16)	221 more per 1,000 (from 46 more to 501 more)	⊕⊕○○ LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI (MD below 0 favours metformin)												
10 ^a	randomised trials	serious ^b	very serious ^k	not serious	not serious	None detected ^d	340	341	-	MD 1.11 lower (1.62 lower to 0.6 lower)	⊕⊕○○ LOW	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - percentage of clinically relevant weight gain (OR below 1 favours intervention) ^m												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ⁿ	randomised trials	very serious ^o	very serious ⁱ	not serious	serious ^p	publication bias strongly suspected ^j	4/34 (11.8%)	18/35 (51.4%)	OR 0.11 (0.03 to 0.41) ^q	410 fewer per 1,000 (from 212 fewer to 483 fewer)	⊕○○○ VERY LOW	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects												
5 ^r	randomised trials	very serious ^s	serious ^t	not serious	not serious ^u	None detected ^d	The five studies reported on discontinuation (metformin, n=215; placebo, n=211). One of the studies reported discontinuation due to dizziness in metformin group and 3 due to development of diabetes in placebo group; another study reported 11 in the metformin and 8 on placebo discontinued to intolerability; another study reported that 1 in metformin group and 2 in placebo withdrew due to psychosis; a further study reported 3 discontinuations due to nausea and psychosis; the final study reported 5 discontinuations due to psychosis. Only one trial reported diarrhoea was significantly more in the metformin group compared to placebo. Three trials reported no significant difference in moderate adverse events. ^v				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. The ten studies were conducted in China (n=4), Venezuela (n=3), Taiwan (n=1), Sri Lanka (n=1), and the USA (n=1). All studies included participants who had schizophrenia or schizoaffective disorder, and who were taking anti-psychotics. Five of the studies also included diet/nutrition and/or exercise counselling (in both the intervention and placebo group). The interventions ranged between 12 and 24 weeks. Taken from Table 1 in de Silva et al (2016). Although the systematic review (de Silva et al 2016) included studies with adults and children, only the analysis for the adult subgroup was included in this table here.
- b. This has been rated as serious, as there was an unclear risk of bias for blinding in 4 studies, and an unclear risk of bias in drop-out rates in 1 study. This information was taken from supplementary Table 1 in de Silva et al (2016).
- c. This has been rated as very serious, as heterogeneity (I²) was reported to be 85% by de Silva et al 2016 (see Figure 2).
- d. Funnel plots were produced by the authors of the systematic review (de Silva et al 2016), which detected no publication bias. See Figure 8 in de Silva et al (2016).
- e. This information was taken from Figure 2 in de Silva et al (2016).
- f. The studies included in the systematic review (Mizuno et al 2014) defined this as between 5 and 10%. See Table S2 in Mizuno et al (2014).
- g. Two of the studies were conducted in China, 1 in Taiwan, and 1 in the USA, with participants who had either schizophrenia or schizoaffective disorder. The studies were between 12 and 24 weeks in duration. Taken from Table 1 in Mizuno et al (2014).
- h. This has been rated as serious, as 2 of the 4 studies had an unclear risk of bias for masking of outcome assessment. Taken from Tables 1 & S1 in Mizuno et al (2014).
- i. This has been rated as very serious, as heterogeneity (I²) was not provided for this particular analysis by the authors of the systematic review (Mizuno et al 2014), and heterogeneity was generally very high for the metformin studies. See Tables 1 and S3 in Mizuno et al (2014).
- j. Funnel plots produced by the authors of the systematic review (Mizuno et al 2014) showed possible publication bias. See Figure S9 in Mizuno et al (2014).
- k. This has been rated as very serious, as heterogeneity (I²) was reported to be 86% by Silva et al 2016 (see Figure 3).
- l. This information was taken from Figure 3 in de Silva et al (2016).
- m. This was defined as over 7% weight gain in the studies included in the systematic review (Mizuno et al 2014). These were primarily prevention studies. See Table S3 in Mizuno et al (2014).
- n. The studies were conducted in Iran and China, with participants who had either schizophrenia or schizoaffective disorder, and were taking an anti-psychotic. The studies were both 12 weeks long. Taken from Table 1 in Mizuno et al (2014).
- o. This has been rated as very serious, as one of the studies had an unclear risk for masking of outcome assessment, and had high drop-out rates in the metformin group. Taken from Tables 1 & S1 in Mizuno et al (2014).
- p. This has been rated as serious, as the number of participants was very low.
- q. This information was taken from Table S3 in Mizuno et al (2014).
- r. The 5 studies were conducted in China (n=3), Sri Lanka (n=1), and the USA (n=1). All studies included participants who had schizophrenia or schizoaffective disorder, and who were taking anti-psychotics. Three of the studies also included diet/nutrition and/or exercise counselling (in both the intervention and placebo group). The interventions ranged between 12 and 24 weeks. Taken from Table 1 in de Silva et al (2016).
- s. This has been rated as very serious, as 3 of the studies had an unclear risk for blinding. This information was taken from Supplementary Table 1 in de Silva et al (2016).
- t. This has been rated as serious, as data were not pooled but did not appear consistent between the 5 included studies.

u. This has been rated as not serious, as even though data were not pooled, the sample size was sufficient..

v. This information was taken from page 4 in de Silva et al (2016).

Table 2: Amantadine vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Amantadine compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
2 ^a	randomised trials	very serious ^b	not serious ^c	not serious	very serious ^d	none detected ^e	71	73	-	MD 2.27 lower (4.76 lower to 0.23 higher)	⊕○○○ VERY LOW	CRITICAL
Change in weight - percentage of clinically relevant weight loss ^f												
1 ^g	randomised trials	very serious ^h	not serious	not serious	serious ⁱ	none detected ^e	7/59 (11.9%)	3/64 (4.7%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - percentage of clinically relevant weight gain												
1 ^g	randomised trials	very serious ^h	not serious	not serious	serious ⁱ	none detected ^e	5/59 (8.5%)	6/64 (9.4%)	not estimable		⊕○○○ VERY LOW	IMPORTANT
Reduced sedentary behaviour - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects												
1 ^j	randomised trials	serious ^k	not serious	not serious	very serious ^l	none detected ^e	Amantadine, n=12; placebo, n=9. One patient randomized to amantadine withdrew from the study due to significant worsening of psychosis. See page 28 in Gierisch et al (2013).				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. Both studies were conducted in the USA, with participants with schizophrenia or related disorders, and bipolar disorder, who were taking olanzapine. The studies lasted 8 and 12 weeks respectively. Taken from Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 40% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as very serious, as the number of participants is low, and the confidence interval includes both 'no effect' and appreciable benefit.
- e. Funnel plots were not produced by the author of the systematic review (Mizuno et al 2014) due to the small number of studies.
- f. The study included in the systematic review (Mizuno et al 2014) defined this as over 7% weight loss/gain. See Table S2 in Mizuno et al (2014).
- g. The study was conducted in the USA, with participants with schizophrenia or related disorders, and bipolar disorder, who were taking olanzapine. The study lasted 8 weeks. Taken from Table 1 in Mizuno et al (2014).
- h. This has been rated as very serious, as the study had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- i. This has been rated as serious, as the number of participants was low, and the effect was reported not to be statistically significant by the authors of the systematic review, with no confidence intervals provided. Taken from Table S2 in Mizuno et al (2014).
- j. Gierisch et al (2013) identified one study that reported on adverse effects. The study was conducted in the USA, and included psychiatric patients with schizophrenia, schizoaffective disorder or bipolar disorder who had gained weight due to olanzapine.
- k. This has been rated as serious, as there was an unclear risk of bias for masking of outcome assessment. This information was taken from the individual study included in the systematic review (Gierisch et al 2013).
- l. This has been rated as very serious due to the very low number of participants.

Table 3: Aripiprazole vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Aripiprazole compared to placebo for people with SMD who are overweight or obese

Setting: outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	aripiprazole	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
3 ^a	randomised trials	very serious ^b	not serious ^c	not serious	not serious	none detected ^d	138	128	-	MD 2.13 lower (2.87 lower to 1.39 lower) ^e	⊕⊕○○ LOW	CRITICAL
Change in weight - percentage of clinically relevant weight loss ^f												
1 ^g	randomised trials	very serious ^h	not serious	not serious	not serious	none detected ^d	16/107 (15.0%)	3/99 (3.0%)	not estimable ⁱ		⊕⊕○○ LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - percentage of clinically relevant weight gain ^f												
1 ^g	randomised trials	very serious ^h	not serious	not serious	not serious	none detected ^d	2/107 (1.9%)	2/99 (2.0%)	not estimable ^j		⊕⊕○○ LOW	CRITICAL
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	aripiprazole	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of adverse events/side-effects												
1 ^k	randomised trials	very serious ^l	not serious	not serious	serious ^m	none detected ⁿ	One participant in the placebo arm and five in the aripiprazole arm discontinued the trial due to adverse effects. However, 0 out of 99 patients in the placebo group and 10 out of 108 patients in the aripiprazole group experienced a serious adverse effect. ^o				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. Two of the studies were conducted in the USA, and 1 in Austria, with participants who had either schizophrenia or schizoaffective disorders, and were taking either clozapine or olanzapine. The studies ranged between 8 and 16 weeks. See Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as all 3 studies had an unclear risk for masking of outcome assessment, and 1 study had uneven drop-out rates. See Table S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Mizuno et al 2014 (see Table 2).
- d. A funnel plot was produced by the authors of the systematic review (Mizuno et al 2014), and no publication bias was detected (see Figure S9).
- e. This information was taken from Table 2 in Mizuno et al (2014).
- f. The study included in the systematic review (Mizuno et al 2014) defined this as over 7% weight loss/gain. The weight gain studies were mostly prevention studies. See Tables S2 & S3 in Mizuno et al (2014).
- g. The study was conducted in Austria, with participants who had either schizophrenia or schizoaffective disorder, and were taking clozapine. The study was 16 weeks long. See Table 1 in Mizuno et al (2014).
- h. This has been rated as very serious, as the study had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- i. Even though the effect size was not reported by the authors of the systematic review (Mizuno et al 2014), the effect was reported to be statistically significant. See Table S2 in Mizuno et al (2014).
- j. Even though the effect size was not reported by the authors of the systematic review (Mizuno et al 2014), the effect was reported to be not statistically significant. See Table S3 in Mizuno et al (2014).
- k. Gierisch et al (2013, 2014) reported adverse events for aripiprazole in their systematic review. They identified 1 study, which was conducted in Austria, with participants who had schizophrenia and were taking clozapine, and had experienced weight gain.
- l. This has been rated as very serious, as the study had an unclear risk for masking of outcome assessment (see Gierisch et al 2013, 2014)
- m. This has been rated as serious, as results were not pooled and it was not reported whether any differences were statistically significant.
- n. Funnel plots were not produced by the authors of the systematic review (Gierisch et al 2013), and so no publication bias was detected.

o. This information was taken from page 27 in Gierisch et al (2013).

Table 4: Fluoxetine vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Fluoxetine compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography: Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	fluoxetine	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
2 ^a	randomised trials	very serious ^b	not serious ^c	not serious	very serious ^d	none detected ^e	30	30	-	MD 0.75 higher (1.76 lower to 3.26 higher) ^f	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/ attenuation/prevention of weight gain - percentage of clinically relevant weight gain ^g												
1 ^h	randomised trials	serious ⁱ	not serious	not serious	very serious ^j	none detected ^e	9/15 (60.0%) ^k	9/15 (60.0%)	not estimable ^k		⊕○○○ VERY LOW	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. The 2 studies were conducted in Israel and the USA respectively, with participants who had schizophrenia or schizoaffective disorder and were taking olanzapine. The studies were 8 and 16 weeks in duration respectively. See Table 1 in Mizuno et al (2014).

- b. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- c. This was rated as not serious, as heterogeneity (I^2) was reported to be 0% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as very serious, as the number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.
- e. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014) due to the small number of studies.
- f. This information was taken from Table 2 in Mizuno et al (2014).
- g. The study included in the systematic review (Mizuno et al 2014) defined this as over 7% weight gain. See Table S3 in Mizuno et al (2014).
- h. The study was conducted in Israel, with participants who had schizophrenia or schizoaffective disorder and were taking olanzapine. The study was 8 weeks in duration. See Table 1 in Mizuno et al (2014).
- i. This has been rated as serious, as the study had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- j. This has been rated as very serious, as the number of participants is very low.
- k. This information was taken from Table S3 in Mizuno et al (2014).

Table 5: Nizatidine vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Nizatidine compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	nizatidine	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
4 ^a	randomised trials	very serious ^b	very serious ^c	not serious	serious ^d	none detected ^e	171	170	-	MD 2.03 lower (4.53 lower to 0.47 higher)	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/ attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	nizatidine	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ^h	randomised trials	serious ⁱ	not serious	not serious	very serious ^j	none detected ^k	The study reported that three patients (out of 54) discontinued the study due to adverse effects (two in the nizatidine treated group). ^l				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Two of the studies were conducted in Turkey, and 2 in the USA, with participants who had either schizophrenia, schizoaffective disorder or schizophreniform disorder, and were taking either olanzapine or quetiapine. The studies ranged between 8 and 16 weeks. One of the studies gave two different doses of nizatidine (300/600 mg). See Table 1 in Mizuno et al (2014).

b. This has been rated as very serious, as all 4 studies had an unclear risk of bias for masking of outcome assessment, and 1 of the studies had high drop-out rates. See Tables 1 & S1 in Mizuno et al (2014).

c. This has been rated as very serious, as heterogeneity (I²) was reported to be 97% by Mizuno et al 2014 (see Table 2).

d. This has been rated as serious, as the confidence intervals include both 'no effect' and appreciable benefit and harm.

e. Funnel plots were produced by the authors of the systematic review (Mizuno et al 2014), which detected no (or just a very small effect) of publication bias. See Figure S9 in Mizuno et al (2014).

h. Gierisch et al (2013) found 1 study that reported on adverse events for nizatidine. The study was conducted in the USA, with participants with schizophrenia, who had been taking olanzapine.

i. This has been rated as serious, as masking of outcome assessment was not clearly reported.

j. This has been rated as very serious, as the number of participants was very low, and statistical significance was not reported.

k. Funnel plots were not produced by the authors of the systematic review (Gierisch et al 2013), as only one study was included.

^l This information was taken from page 30 in Gierisch et al (2013).

Table 6: Orlistat vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Orlistat compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography: Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	orlistat	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (kg)												
1 ^a	randomised trials	serious ^b	not serious	not serious	very serious ^c	none detected ^d	Intervention, n=31; placebo, n=32. Mean change in kg was -1.25 ± SD 4.33 in the intervention group, and 0.44 ± SD 3.73 in the placebo group. ^e				⊕○○○ VERY LOW	CRITICAL
Change in weight - percentage of clinically relevant weight loss [†]												
1 ^a	randomised trials	serious ^b	not serious	not serious	very serious ^c	none detected ^d	5/31 (16.1%)	2/32 (6.3%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

a. The study was conducted in Finland, with participants with SMD (unspecified) who were taking clozapine or olanzapine. The study was 16 weeks in duration. See Table 1 in Mizuno et al (2014).

- b. This has been rated as serious, as the study had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- c. This has been rated as very serious, as the number of participants is very low.
- d. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014), as only one study was included.
- e. This information was taken from Table 2 in Mizuno et al (2014).
- f. The study included in the systematic review (Mizuno et al 2014) defined this as over 5% weight loss. See Table S2 in Mizuno et al (2014).

Table 7: Reboxetine vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Reboxetine compared to placebo for people with SMD who are overweight or obese

Setting: inpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

3

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	reboxetine	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
2 ^a	randomised trials	very serious ^b	not serious ^c	not serious	serious ^d	none detected ^e	41	38	-	MD 1.9 lower (3.07 lower to 0.72 lower) ^f	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - percentage of clinically relevant weight gain (OR below 1 favours intervention) ^g												
2 ^a	randomised trials	very serious ^b	not serious	not serious	serious ^h	none detected ^e	8/41 (19.5%)	20/38 (52.6%)	OR 0.22 (0.08 to 0.60) ⁱ	330 fewer per 1,000 (from 126 fewer to 445 fewer)	⊕○○○ VERY LOW	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. Both studies were conducted in Israel, with participants who had schizophrenia and were taking olanzapine. The studies were both 6 weeks in duration. See Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as one of the studies had high drop-out rates (30.5%). See Tables 1 and S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) in these studies was reported to be 0% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as serious, as the number of participants is very low.
- e. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014) due to the small number of studies.
- f. This information was taken from Table 2 in Mizuno et al (2014).
- g. The studies included in the systematic review (Mizuno et al 2014) defined this as over 7% weight gain. These studies were primarily prevention studies. See Table S3 in Mizuno et al (2014).
- h. This has been rated as serious, as the number of participants is very low.
- i. This information was taken from Table S3 in Mizuno et al (2014).

Table 8: Rosiglitazone vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Rosiglitazone compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography: Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	rosiglitazone	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
2 ^a	randomised trials	very serious ^b	not serious ^c	not serious	very serious ^d	none detected ^e	22	25	-	MD 0.26 higher (1.83 lower to 2.35 higher) ^f	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. The 2 studies were conducted in Venezuela and the USA respectively, with participants who had schizophrenia or schizoaffective disorder, and were taking either clozapine or olanzapine. The studies were 8 and 12 weeks in duration respectively. See Table 1 in Mizuno et al (2014).

- b. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment. See Tables 1 & S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as very serious, as the number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.
- e. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014) due to the low number of studies.
- f. This information was taken from Table 2 in Mizuno et al (2014).

Table 9: Sibutramine vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Sibutramine compared to placebo for people with SMD who are overweight or obese

Setting: outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	sibutramine	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
3 ^a	randomised trials	very serious ^b	not serious ^c	not serious	serious ^d	none detected ^e	34	32	-	MD 2.86 lower (4.72 lower to 1.01 lower) ^f	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI (see footnotes for ‘change in weight’)												
									not estimable		-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. Two of the studies were conducted in the USA, and 1 in Austria. They included participants with schizophrenia or schizoaffective disorder. Participants were taking anti-psychotics (e.g. olanzapine or clozapine). Two of the studies were 12 weeks in duration, and 1 study was 24 weeks in duration. See Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as all 3 studies had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- c. This was rated as not serious, as heterogeneity (I²) was reported to be 49% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as serious, as the number of participants is very low.
- e. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014) due to the small number of studies.
- f. This information was taken from Table 2 in Mizuno et al (2014).

Table 10: Topiramate vs. placebo for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Topiramate compared to placebo for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	topiramate	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in weight (MD below 0 favours intervention)												
2 ^a	randomised trials	very serious ^b	not serious ^c	not serious	serious ^d	none detected ^e	66	74	-	MD 5.2 lower (9.55 lower to 0.84 lower) ^f	⊕○○○ VERY LOW	CRITICAL
Change in weight - percentage of clinically relevant weight loss (OR above 1 favours intervention) ^g												
1 ^h	randomised trials	serious ⁱ	not serious	not serious	very serious ^j	none detected ^e	5/33 (15.2%)	0/40 (0.0%)	OR 7.76 (0.85 to 70.78)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI (see footnotes for 'change in weight')												
									not estimable		-	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain (see footnotes)												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	topiramate	placebo	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects (see footnotes)												
-	-	-	-	-	-	-	-	-	--	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. The 2 studies were conducted in South Korea and India respectively, with participants who had schizophrenia and who were taking an anti-psychotic. Both studies were 12 weeks in duration. One of the studies assessed two different doses of topiramate (100/200 mg). See Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as both studies had an unclear risk of bias for masking of outcome assessment. Taken from Tables 1 and S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Mizuno et al 2014 (see Table 2).
- d. This has been rated as serious, as the number of participants is low.
- e. Funnel plots were not produced by the authors of the systematic review (Mizuno et al 2014) due to the small number of studies.
- f. This information was taken from Table 2 in Mizuno et al (2014).
- g. In the study included in the systematic review (Mizuno et al 2014), this was defined as over 10% weight loss. See Table S2 in Mizuno et al (2014).
- h. The study was conducted in South Korea, with participants who had schizophrenia and who were taking an anti-psychotic. The study was 12 weeks in duration, and assessed two different doses of topiramate (100/200 mg). See Table 1 in Mizuno et al (2014).
- i. This has been rated as serious, as the study had an unclear risk of bias for masking of outcome assessment. See Table S1 in Mizuno et al (2014).
- j. This has been rated as very serious, as the number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit.

Table 11: Anti-psychotic switching from olanzapine vs. olanzapine for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Anti-psychotic switching from olanzapine compared to olanzapine for people with SMD who are overweight or obese

Setting: outpatients

Bibliography: Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-psychotic switching from olanzapine	olanzapine	Relative (95% CI)	Absolute (95% CI)		
Change in weight												
4 ^a	randomised trials	serious ^b	serious ^c	not serious	serious ^d	none detected ^e	Switching to aripiprazole: Patients (n=173) who switched to aripiprazole experienced significantly more weight loss than those remaining on olanzapine (-1.84 vs. +1.31 kg, p=0.001), a difference of small magnitude between groups. Switching to quetiapine: Mean weight change between olanzapine and quetiapine were not significant (+0.99 vs. -0.82, p=0.089, n=133). Neither of the two studies that examined switching to a different form of olanzapine showed significant effects on weight control. Results for the study that involved switching to orally disintegrating olanzapine: mean weight gain of +2.08 vs. +1.42, p=0.39, n=149. Study that involved switching to long-acting intramuscular injection of olanzapine: Patients (n=921) taking both formulations of olanzapine experienced statistically significant increases in weight compared with baseline (+1.3 [injection] vs. +1.3 [oral]); however, there were no between-group differences (p=0.34). ^f				⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-psychotic switching from olanzapine	olanzapine	Relative (95% CI)	Absolute (95% CI)		
Maintenance of weight change/ attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events/side-effects												
4 ^a	randomised trials	serious ^b	serious ^c	not serious	serious ^d	none detected ^e	Switching to orally disintegrating olanzapine (ODO) (n=149): Two patients in each group discontinued treatment due to adverse effects; two patients in the ODO group experienced a serious adverse effect. Switching to long-acting intramuscular injection of olanzapine (n=921): A total of 57 patients discontinued use due to adverse effects, but there were no differences between groups (p-value NR). Switching to quetiapine (n=133): Significantly more subjects in the olanzapine group completed 24 weeks of treatment than the quetiapine group (70.3% vs. 43. 1%, p=0.002); discontinuation due to psychiatric adverse effects was higher in the quetiapine-treated group (p=0.003); however, no significant differences were observed for nonpsychiatric discontinuations (p-value NR); there were no significant differences in hospitalization rates (7.69% in the quetiapine group vs. 1.47% in the olanzapine group, p-value not reported); no other serious adverse events were reported. Switching to aripiprazole (n=173): A total of 15 participants discontinued treatment due to adverse effects (7 aripiprazole-treated, 8 olanzapine treated); six participants treated with aripiprazole experienced a serious adverse effect compared with nine in the olanzapine-treated group (p-value NR). ^f				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

- a. The 4 studies were conducted in several countries worldwide: 1 was conducted in the USA; 1 in the USA, Canada, Mexico and countries in Europe; and 2 studies were multinational (one of which was conducted in 26 unspecified countries). The studies involved participants with schizophrenia or associated disorders, and bipolar disorder. Two of the studies involved switching from standard olanzapine to different forms of olanzapine (one orally disintegrating olanzapine, and one long-acting injectable olanzapine), 1 study involved switching from olanzapine to aripiprazole, and the other study involved switching from olanzapine to quetiapine. See Table F1 and page 31 in Gierisch et al 2013.
- b. This has been rated as serious, as there was an unclear masking of outcome assessment in several of the studies.
- c. This has been rated as serious, since heterogeneity could not be formally tested (as; results were not pooled), and results appeared inconsistent between the different studies. See page 31 in Gierisch et al 2013.
- d. This has been rated as serious, as the sample size was low in 3 of the 4 included studies.
- e. Funnel plots were not produced by the authors of the systematic review (Gierisch et al 2013) due to the small number of studies.
- f. This information was taken from pages 31 and 32 in Gierisch et al (2013).

Table 12: Short-term lifestyle interventions (6 months and under) vs. care as usual for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Short-term lifestyle interventions (under 6 months) compared to care as usual for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography:

Naslund JA et al. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: A systematic review and meta-analysis. General Hospital Psychiatry. 2017; 47: 83-102

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Review 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	short-term lifestyle interventions (under 6 months)	care as usual	Relative (95% CI)	Absolute (95% CI)		
Change in weight (kg)(MD below 0 favours intervention)												
10 ^a	randomised trials	very serious ^b	very serious ^c	not serious	not serious	publication bias strongly suspected ^d	391	387	-	MD 0.2 lower (0.34 lower to 0.05 lower) ^e	⊕○○○ VERY LOW	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	short-term lifestyle interventions (under 6 months)	care as usual	Relative (95% CI)	Absolute (95% CI)		
Frequency of adverse events / side-effects												
3 [†]	randomised trials	very serious ^g	not serious ⁿ	not serious	not serious	none detected [†]	The three studies that reported discontinuations due to serious or non-serious adverse effects (n=263) found no difference between groups. For the other studies included in Gierisch et al (2013, 2014) that reported adverse effects, none reported significant differences between conditions in serious adverse effects.			⊕⊕○○ LOW	IMPORTANT	

CI: Confidence interval; **MD:** Mean difference

Explanations

- The 10 studies were conducted in the USA (n=5), Spain (n=2), Taiwan (n=1), China (n=1), and Thailand (n=1). The interventions were as follows: behavioural treatment consisting of group sessions (n=7) or individual sessions (n=2), which focused on diet, nutrition, weight management techniques, education and physical activity (one study included both/either group and individual sessions), CBT (n=1), and a weight management programme (n=1). The interventions ranged between 8 weeks and 6 months in length. Studies included participants with schizophrenia, schizoaffective disorder or schizophrenia spectrum disorders (n=9), bipolar disorder (n=2), MDD (n=1), PTSD (n=1; sub-set of participants), undefined SMD (n=1), or people taking anti-psychotics (n=1) (some studies included more than one of these participant groups). All participants in the studies were classed as overweight or obese (BMI of over 25, or over 23 in Asian populations). See Table 2 in Naslund et al (2017).
- This has been rated as very serious, as 5 of the 10 studies did not meet one or more of the three criteria (i.e. randomization, masking of outcome assessment, drop-out rates below 30%). In 3 studies, there was no masking of outcome assessment, and 3 studies had drop-out rates above 30%. Taken from Table 3 in Naslund et al (2017).
- This has been rated as very serious, as heterogeneity (I²) was reported to be 90% by Naslund et al 2017 (see Figure 3a).
- Funnel plots were produced by the authors of the systematic review (Naslund et al 2017), which suggested moderate to low risk of publication bias. In statistical tests, the Egger test suggested possible publication bias, whereas the Begg-Mazumdar test did not. See Figure 2 in Naslund et al (2017).
- This information was taken from Figure 3a in Naslund et al (2017).
- Three studies included in Gierisch et al (2013, 2014) assessed adverse events. The studies were conducted in the USA (n=2), and countries in Asia (n=1), with participants who had schizophrenia. The interventions included behavioural therapy sessions, covering diet, nutrition, exercise, lifestyle and self-monitoring. Interventions ranged between 12 and 24 weeks. See Table F-1 in Gierisch et al 2013.

- g. This has been rated as very serious, as 1 of the studies had an unclear risk for masking of outcome assessment, and 1 study had high drop-out rates. This information was taken from the individual studies included in the systematic review (Gierisch et al 2013).
- h. This has been rated as not serious, as there is no reason to suspect heterogeneity; however heterogeneity was not formally assessed for this outcome. See Gierisch et al (2013), page 26.
- i. Funnel plots produced by the authors of the systematic review (Gierisch et al 2013) to assess publication bias did not demonstrate evidence of publication bias. See Gierisch et al (2013), page 26.

Table 13: Long-term lifestyle interventions (12 months and over) vs. care as usual for people with SMD who are overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Long-term lifestyle interventions (12 months and over) compared to care as usual for people with SMD who are overweight or obese

Setting: inpatients and outpatients

Bibliography: Naslund JA et al. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: A systematic review and meta-analysis. General Hospital Psychiatry. 2017; 47: 83-102

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	long-term lifestyle interventions (over 12 months)	care as usual	Relative (95% CI)	Absolute (95% CI)		
Change in weight (kg) (MD below 0 favours intervention)												
6 ^a	randomised trials	serious ^b	not serious ^c	not serious	not serious	publication bias strongly suspected ^d	543	532	-	MD 0.24 lower (0.36 lower to 0.12 lower) ^e	⊕⊕○○ LOW	CRITICAL
Change in weight - achieving clinically significant (5% or greater) weight loss (OR above 1 favours intervention) ^f												
5 ^g	randomised trials	serious ^h	not serious ⁱ	not serious	not serious	publication bias strongly suspected ^d	158/479 (33.0%)	108/463 (23.3%)	OR 1.62 (1.21 to 2.16) ^j	97 more per 1,000 (from 36 more to 163 more)	⊕⊕○○ LOW	CRITICAL
Maintenance of weight change/attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Frequency of adverse events / side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. The 6 studies were conducted in the USA (n=5), and the UK (n=1). The interventions were as follows: behavioural / weight management interventions consisting of group sessions (n=5) or individual sessions (n=6), which focused on diet, nutrition, weight management techniques, education and physical activity / fitness (several studies included both/either group and individual sessions, often phased at different time points). The interventions ranged between 12 and 18 months in length. Studies included participants with schizophrenia, schizoaffective disorder or schizophrenia spectrum disorders (n=6), bipolar disorder (n=4), MDD (n=3), other psychosis (n=2), PTSD (n=1; only 2% of participants in one study), unspecified other (n=1) (several studies included more than one of these participant groups). All participants in the studies were classed as overweight or obese (BMI of over 25, or over 23 in Asian populations). See Table 2 in Naslund et al (2017).
- b. This has been rated as serious, as one of the studies did not have masking of outcome assessment, and had drop-out rates of above 30% (32%). See Table 3 in Naslund et al (2017).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Naslund et al 2017 (see Figure 3b).
- d. Funnel plots were produced by the authors of the systematic review (Naslund et al 2017), which suggested moderate to low risk of publication bias. In statistical tests, the Egger test suggested possible publication bias, whereas the Begg-Mazumdar test did not. See Figure 2 in Naslund et al (2017).
- e. This information was taken from Figure 3b in Naslund et al (2017).
- f. This outcome was included by Naslund et al (2017), since modest ≥5% weight loss is associated with reduction in cardiovascular risk among overweight and obese individuals. See page 84 in Naslund et al 2017.
- g. All 5 studies were conducted in the USA. The interventions were as follows: behavioural / weight management interventions consisting of group sessions (n=3) or individual sessions (n=5), which focused on diet, nutrition, weight management techniques, education and physical activity / fitness (several studies included both/either group and individual sessions, often phased at different time points). The interventions ranged between 12 and 18 months in length. Studies included participants with schizophrenia, schizoaffective disorder or schizophrenia spectrum disorders (n=5), bipolar disorder (n=5), MDD (n=3), affective psychosis (n=1), PTSD (n=1; only 2% of participants in one study), unspecified other (n=2; 6 & 8 % of participants respectively) (all studies included more than one of these participant groups). All participants in the studies were classed as overweight or obese (BMI of over 25, or over 23 in Asian populations). See Table 2 in Naslund et al (2017).
- h. This has been rated as serious, as one of the studies had a very high drop-out rate (49%). See Table 3 in Naslund et al (2017).
- i. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Naslund et al 2017 (see Figure 4).
- j. This information was taken from Figure 4 in Naslund et al (2017).

GRADE Evidence Tables (at risk of becoming overweight or obese)

Table 14: Lifestyle interventions vs care as usual for people with SMD who are at risk of becoming overweight or obese

Author(s): Maya Semrau

Date: April 2018

Question: Lifestyle interventions compared to care as usual for people with SMD who are at risk of becoming overweight or obese (i.e. at anti-psychotic initiation)

Setting: inpatients and outpatients

Bibliography: Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	lifestyle interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
Change in weight (kg) (MD below 0 favours intervention)												
4 ^a	randomised trials	very serious ^b	not serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	79	60	-	MD 2.95 lower (4.38 lower to 1.52 lower) ^g	⊕○○○ VERY LOW	CRITICAL
Mean BMI (kg/m2) or change in BMI												
3 ^h	randomised trials	very serious ⁱ	serious ^j	serious ^d	serious ^e	publication bias strongly suspected ^f	69	52	-	MD 0.95 lower (1.51 lower to 0.4 lower)	⊕○○○ VERY LOW	CRITICAL
Maintenance of weight change - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Attenuation/prevention of weight gain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Reduced sedentary behaviour - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	lifestyle interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. The 4 studies were conducted in Australia, Germany, Italy and Spain respectively. Participants were included with schizophrenia (n=4), schizoaffective disorder (n=4), schizophreniform disorder (n=2), bipolar affective disorder (n=1), delusional disorder (n=1), brief reactive psychosis (n=1), psychosis not otherwise specified (n=1), and depression (n=1). Interventions in 3 of the studies included nutrition interventions plus exercise or exercise education, and 1 included only nutrition; 3 of the interventions were delivered by dietitians, and 1 by a clinical psychologist and/or nurse; 3 interventions were delivered through individual sessions, and 1 as group sessions. See Table DS1 in Teasdale et al (2017).
- b. This has been rated as very serious, as 3 of the 4 studies did not have masking of outcome assessment, and 2 of the studies had high drop-out rates. This information was taken from Table DS2 in Teasdale et al (2017), and from the individual studies included in the systematic review.
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 34% by Teasdale et al 2017 (see Table 1).
- d. This has been rated as serious, since even though only those studies were included in the table here that looked at prevention of weight gain in people who had just started anti-psychotic treatment, the majority of these participants were already overweight. This information was obtained from the first author of the systematic review (SB Teasdale).
- e. This has been rated as serious, as the number of participants is low.
- f. Teasdale et al (2017) reported that there was evidence of publication bias, although when adjusting for publication bias results remained statistically significant. See page 112 in Teasdale et al 2017.
- g. This information was taken from Table 1 in Teasdale et al (2017).
- h. The 3 studies were conducted in Australia, Germany and Spain respectively. Participants were included with schizophrenia (n=3), schizoaffective disorder (n=3), schizophreniform disorder (n=2), bipolar affective disorder (n=1), delusional disorder (n=1), brief reactive psychosis (n=1), psychosis not otherwise specified (n=1), and depression (n=1). Interventions in 2 of the studies included nutrition interventions plus exercise or exercise education, and 1 included only nutrition; 2 of the interventions were delivered by dietitians, and 1 by a clinical psychologist and/or nurse; 2 interventions were delivered through individual sessions, and 1 as group sessions. See Table DS1 in Teasdale et al (2017).
- i. This has been rated as very serious, as all 3 studies did not have masking of outcome assessment, and 2 studies had high drop-out rates. This information was taken from Table DS2 in Teasdale et al (2017), and from the individual studies included in the systematic review.
- j. This has been rated as serious, as heterogeneity (I²) was reported to be 66% by Teasdale et al 2017 (see Table 1).

Additional evidence not mentioned in GRADE tables⁴

Agarwal et al (2017) conducted a Cochrane meta-analysis (published as conference proceedings so far) to determine the effects of pharmacological interventions aimed at reduction or prevention of weight gain in schizophrenia. Forty-four randomized controlled trials met the inclusion criteria for this review. Metformin (weight: $n = 106$, 3 RCTs, MD -3.40 kg CI -6.71 to -0.08 ; BMI: $n = 106$, 3 RCTs, MD -1.29 , CI -2.29 to -0.29), reboxetine (weight: $n = 79$, 2 RCTs MD -1.90 , CI -3.07 to -0.72 ; BMI: $n = 79$, 2 RCTs, MD -0.68 , CI -1.08 to -0.28), and reboxetine-betahistine (weight: $n = 32$, 1 RCT MD -2.75 , CI -4.94 to -0.56 ; BMI: $n = 32$, 1 RCT, MD -0.74 , CI -1.35 to -0.13) were found to have a modest effect in preventing weight gain and change in BMI while topiramate ($n = 67$, 1 RCT, MD -2.45 kg/m² CI -4.39 to -0.51 kg/m²) prevented a change in body mass index (BMI) in patients started on antipsychotic treatment. In terms of treatments for weight loss, we found significantly greater reduction in weight in patients treated with metformin ($n = 541$, 7 RCTs, MD -3.42 kg CI -4.96 to -1.88 kg), aripiprazole ($n = 236$, 2 RCTs, MD -2.00 kg CI -2.96 to -1.03 kg), nizatidine ($n = 113$, 3 RCTs, MD -4.42 kg CI -8.10 to -0.73 kg), sibutramine ($n = 68$, 4 RCTs, MD -5.42 kg CI -8.33 to -2.51 kg), and topiramate (200 mg but not 100 mg) ($n = 37$, 1 RCT, MD -5.05 kg CI -7.67 to -2.43 kg), and significantly greater reduction in BMI in patients treated with metformin ($n = 578$, 8 RCTs, MD -1.31 kg/m² CI -1.85 to -0.78 kg/m²), sibutramine ($n = 68$, 4 RCTs, MD -1.09 kg/m² CI -1.88 to -0.30 kg/m²), and topiramate (200 mg but not 100 mg) ($n = 37$, 1 RCT, MD -1.91 kg/m² CI -3.11 to -0.71 kg/m²) compared with placebo. Importantly, none of the adjunctive treatment strategies resulted in worsening of mental status or in higher dropout rates; topiramate may in fact be associated with improvement in clinical status while reboxetine and reboxetine-betahistine might decrease depressive symptoms. Among the agents that led to a significant decrease in weight, metformin, topiramate, nizatidine, reboxetine, reboxetinebetahistine, and sibutramine did not differ compared to placebo with respect to the frequency of adverse effects, while aripiprazole resulted in significantly higher occurrence of nausea and anxiety. Authors' conclusions: Accumulating evidence supports the safe use of pharmacological interventions to achieve modest weight loss. Metformin has the most evidence for use both for prevention as well as treatment of weight gain in schizophrenia. Other agents showing positive effects include aripiprazole, topiramate, nizatidine, reboxetine, reboxetine-betahistine, and sibutramine. However, interpretation for these agents is limited by the small number of studies, small sample size, and short study duration. Future studies adequately powered, with longer treatment duration will be needed in further evaluating the efficacy and safety of interventions for managing weight gain.

Liu et al (2015) conducted a systematic review about the use of metformin to treat clozapine-induced weight gain in adults with schizophrenia. Six studies with a pooled sample of 207 treatment-group patients and 207 control-group patients were included – three double-blind, placebo-controlled RCTs and three RCTs that did not use placebo controls and were not blinded. The meta-analysis found that compared to the control condition, patients receiving metformin experienced significantly greater reductions in body weight (mean difference [MD] $= -2.89$ kg, 95% CI: -4.20 to -1.59 kg) and body mass index (BMI) (MD $= -0.81$, 95% CI: -1.16 to -0.45), but there was no significant difference between the groups in the prevalence of side effects. Authors' conclusions: Adjunctive treatment with metformin appears to be effective for treating clozapine-induced weight gain and elevations in BMI in

⁴ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

adult patients with schizophrenia. However, the quality of the evidence about the safety of this treatment is low, follow-up time in the available studies is relatively short, and half of the studies did not employ blinded assessment of outcome measures. Larger studies with placebo controls that follow patients for at least 24 weeks and that make blinded assessments of a range of relevant outcome measures (weight, BMI, blood lipids, insulin resistance, etc.) are needed to confirm these results.

Siskind et al (2016) conducted a systematic-review and meta-analysis of metformin versus placebo for change in weight and metabolic syndrome for people on clozapine without diabetes mellitus. Eight studies, of which three were from Chinese databases, with 478 participants were included. We found that metformin was superior to placebo in terms of weight loss (-3.12kg, 95%CI -4.88kg to -1.37kg) and BMI (-1.18kg/m², 95%CI -1.76kg/m² to -0.61kg/m²). Metformin significantly improved three of the five components of metabolic syndrome; waist circumference, fasting glucose and triglycerides. Sensitivity analysis on study quality and duration did not greatly impact results. Authors' conclusions: Metformin led to clinically meaningful weight loss among people on clozapine, and may reduce the rates of metabolic syndrome. Inclusion of metformin into the treatment protocols of people on clozapine, as tolerated, should be considered.

Andrade et al (2016) in a narrative review of the evidence reported that patients with schizophrenia have increased prevalence rates for many cardiometabolic risk factors; the prevalence and severity of these risks increase after the institution of antipsychotic medication. Nearly 2 dozen different pharmacologic interventions have been trialled to prevent or attenuate antipsychotic-related cardiometabolic changes. Metformin (usually 1,000-1,500 mg/d) has emerged as the best-studied intervention; in short- and intermediate-duration randomized controlled trials, it has been shown to bring about improvements in weight and other anthropometric indices, in fasting sugar and other glycemic control indices, and in total cholesterol and other lipid metabolism indices. Topiramate and aripiprazole are other possible interventions with support in literature; besides improving metabolic outcomes, these drugs may improve indices of psychopathology, as well. Encouraging though the findings are, there are many unanswered questions that require attention in future research.

Baxter et al (2016) explored the strength of evidence for interventions to reduce risk of mortality in people with SMD. Method: In a meta-review of 16 systematic reviews of controlled studies, mortality was the primary outcome (8 reviews). Physiological health measures (body mass index, weight, glucose levels, lipid profiles and blood pressure) were secondary outcomes (14 reviews). Results: Antipsychotic and antidepressant medications had some protective effect on mortality, subject to treatment adherence. Integrative community care programmes may reduce physical morbidity and excess deaths, but the effective ingredients are unknown. Interventions to improve unhealthy lifestyles and risky behaviours can improve risk factor profiles, but longer follow-up is needed. Preventive interventions and improved medical care for comorbid chronic disease may reduce excess mortality, but data are lacking. Author's conclusions: Improved adherence to pharmacological and physical health management guidelines is indicated

Relevant guidelines

The NICE guidelines *Psychosis and schizophrenia in adults: prevention and management* (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014) includes the following relevant recommendations:

- “Physical health”: patients (esp. those taking antipsychotics) should be offered a combined healthy eating and physical activity programme.
- If person has rapid/excessive weight gain, abnormal lipid levels, or problems with blood glucose management, offer intervention in line with NICE guidance (on obesity, lipid modification, preventing diabetes).
- Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity; should be audited annually.
- “Monitoring physical health in primary care” GPs and primary health care professionals should monitor physical health of people with psychosis; comprehensive health checks and refer to relevant NICE guidance on monitoring cardiovascular disease, diabetes, obesity and respiratory disease. Results to be shared with secondary care providers.
- Should identify people who have CVD, high blood pressure, abnormal lipid levels, are obese/at risk of obesity, have diabetes/at risk of diabetes (as indicated by abnormal blood glucose levels), or physically inactive, at the earliest opportunity following relevant NICE guidance for these conditions.
- “Choice of antipsychotic medication”: antipsychotic medication choice considering metabolic side effects (including weight gain and diabetes), cardiovascular (including prolonging the QT interval)
- Baseline measures before starting antipsychotic medication: weight, waist circumference, pulse and blood pressure, fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels, assessment of nutritional status, diet and level of physical activity.

The NICE guidelines *Bipolar disorder: assessment and management* (Clinical guideline [CG185]; Published date: September 2014 Last updated: February 2016) include the following relevant recommendations:

- “Monitoring physical health”: develop and use practice case register to monitor physical health of people with BPD in primary care.
- Included in health check: weight or BMI, diet, nutritional status and level of physical activity cardiovascular status, including pulse and blood pressure metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile.

The NICE guidelines *Depression in adults with a chronic physical health problem: recognition and management* (Clinical guideline [CG91]; Published date: October 2009) include the following relevant recommendations:

- Comment regarding need to monitor "weight, lipid and glucose levels" and "side effects" if prescribing antipsychotic medication.

Cooper et al's (2016) *BAP guidelines* recommended the following for people with psychosis and anti-psychotic drug treatment:

- The measurements below should be assessed before starting an antipsychotic, or as soon as possible afterwards, and then at the intervals indicated.

- Body mass index (BMI) should be used to monitor whether an individual is becoming overweight or obese. This requires frequent measurement of weight during the early stages of treatment: ideally weekly for the first 4–6 weeks and then every 2–4 weeks up to 12 weeks; but, as a minimum, once every 4 weeks for the first 12 weeks' of treatment. Weight (and BMI) should then be assessed at 6 months and at least annually thereafter, unless the clinical situation demands more frequent assessment.
- If there is a change in antipsychotic medication then, when clinically relevant, it is appropriate to re-visit all of the steps outlined above.
- It is important to take ethnicity into account when evaluating BMI results.
- Lifestyle interventions (mostly of the 'behavioural lifestyle intervention' type):
 - Lifestyle interventions are recommended as they have a positive effect in the majority of RCTs. These should almost always be part of the first line of approach and in most circumstances should be continued in addition to any additional intervention.
 - On average, these interventions will reduce existing weight by approximately 3 kg more, and BMI by approximately 1 kg/m² more, than the control treatment.
 - They will attenuate weight gain in first-episode initiations of antipsychotics.
 - There is no clear evidence regarding the optimal duration of engagement with such interventions. Evidence regarding maintenance of effects is limited in both those with long-standing and first episodes of illness. 'Booster sessions' may be required to maintain effects.
 - A limited amount of evidence suggests that programmes work best if designed specifically for those with psychosis and if they combine elements of group and individual patient approaches.
- Antipsychotic switching:
 - Extrapolation from the evidence, below, suggests that switching to one of the antipsychotic medications with lower propensity for weight gain is a strategy that should be considered.
 - Much of the evidence to support antipsychotic switching strategies inevitably comes from meta-analyses of the differential effects of different medications on weight. These data suggest a hierarchy of antipsychotic medications with respect to weight gain, with the following medications appearing to carry the lowest propensity for weight gain: haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride and asenapine (asenapine is only licensed for bipolar mania in the UK).
 - Only four RCTs have directly examined antipsychotic switching for the specific purpose of weight reduction. These supported switching from olanzapine to either aripiprazole or quetiapine with an approximately 3 kg greater weight reduction with switching compared to no change.
 - Clinicians must balance the possible benefit on weight of switching antipsychotic medication against the risks of inducing relapse of core psychotic symptoms.
- Adjunctive aripiprazole:
 - Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine.
 - Three RCTs of the addition of aripiprazole to clozapine or olanzapine, only one of significant size, found a mean difference in weight loss for aripiprazole over placebo of just over 2 kg.

- Extrapolation of this effect to weight gain induced by other antipsychotic medications is not supported by current evidence.
- Adjunctive metformin:
 - In the context of recommendations regarding groups at high risk of diabetes in NICE PH38, metformin should be considered as an adjunct to attenuate or reduce weight gain following antipsychotic medication. It should be emphasised that lifestyle interventions should have been fully explored and the other interventions, above, considered.
 - Metformin has been compared to lifestyle intervention for weight reduction in a large 3-year RCT of people at high risk of diabetes in the general population. Metformin leads to a modest reduction in weight (approximately 2 kg) over the short and long term but is less effective than intensive lifestyle intervention.
 - Its use in certain situations in people at high risk of diabetes is supported by NICE PH38.
 - In people taking antipsychotic medications, short-term trials have shown that metformin reduces weight, compared to placebo, by approximately 3 kg. It attenuates weight gain in first-episode initiations of antipsychotic medication by approximately 5 kg, compared to placebo.
 - There are some risks attached to metformin that require appropriate monitoring (renal function and vitamin B12).
- Interventions not recommended in routine clinical practice for people with SMD:
 - Orlistat has been subject to RCTs in the general population where it reduces weight by approximately 3 kg over 1 year. However, long-term use is extremely limited by high rates of discontinuation. In two trials in psychosis an effect was seen only in men. Clinical experience suggests high rates of discontinuation in this patient group, making it of little value in routine clinical practice.
 - Three out of four RCTs of topiramate as an adjunct to antipsychotics reported statistically significant weight loss, ranging from 1.5 kg to 5 kg. One RCT supports an effect to attenuate weight gain in people with a first episode of psychosis. However, the risk–benefit profile of topiramate is severely limited by its adverse effects.
 - Reboksetine has consistent data from three trials suggesting benefit, but all are from a single research group with no independent replication yet available.
 - Glucagon-like peptide-1 (GLP-1) receptor agonists have been found to be effective for weight reduction in obesity in the general population, and liraglutide has been given marketing authorisation for this use. However, there are no RCT data yet available for this use in people with psychosis taking antipsychotic medications.
 - Non-RCT data give tentative support to the use of bariatric surgery in extreme obesity in a few selected people with schizophrenia. There are no adequate long-term follow-up data available for this population.
 - Amantadine, melatonin and zonisamide have all been subject to RCTs that suggest a beneficial effect. However, available data are too limited to make any recommendation regarding their use.
 - Clinical trials of atomoxetine, dextroamphetamine, famotidine, fluoxetine, fluvoxamine and nizatidine have failed to show benefit.

Hasan et al (2017)'s *World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia – A short version for primary care* recommend the following:

- Monitor the development of metabolic side effects carefully.
- React to metabolic changes. On the basis of the EPA statement, the WFSBP guidelines recommend that a weight gain >7% than baseline occurring within a few months must alert physicians and relatives.
- Provide psychosocial interventions such as awareness programs, diet plans, CBT to reduce weight and increase physical activity.
- Switch to an antipsychotic with a more favourable metabolic profile. However, physicians should be aware that every antipsychotic switch is associated with an increased risk for symptom deterioration or relapse. The WFSBP guidelines recommend aripiprazole and ziprasidone for this purpose, but also other antipsychotics with a more favourable metabolic profile than the one causing the side effects should be considered.
- Add metformin to an ongoing antipsychotic treatment. The full WFSBP guidelines (2013) were inconclusive regarding this recommendation, whereas recent publications provide sufficient data for a recommendation (Mizuno et al. 2014; Wu et al. 2016). However, negative results have been reported and the addition of metformin does not render a strict monitoring and management of metabolic side effect unnecessary.

Also see Taylor et al, *The Maudsley Prescribing Guidelines in Psychiatry* (new edition published in May 2018).

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Fluoxetine may increase the potency of anti-diabetic medication such as **metformin**. Monitor blood glucose control and adjust dosing of anti-diabetic medication accordingly, especially when starting or stopping fluoxetine. Risperidone and clozapine are associated with hyperglycemia and as such, may decrease the efficacy of anti-diabetic medication including **metformin**. Monitor glycemic control and adjust dosing of anti-diabetic medications accordingly.

See Annex for further information.

WHO guidelines for general population

WHO mhGAP

- Dementia module: under "evaluate for other medical issues", asks regarding "cardiovascular risk factors" incl. obesity and "reducing cardiovascular risk factors: incl. weight reducing diet for obesity"
- Psychoses module: Metabolic changes (weight gain, high blood pressure, increased blood sugar and cholesterol) listed in side-effects for medication.

WHO *Guidelines for primary health care in low-resource settings* (2012):

- Tobacco use, unhealthy diet and physical inactivity: shared risk factor for NCD prevention/control priority conditions (CVD, diabetes, chronic respiratory disease and cancer)
- Advise overweight patients to reduce weight by reducing their food intake.
- Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

Related WHO GRC publications:

1. [Global recommendations on physical activity for health](#)
2. [Interventions on diet and physical activity: what works: summary report](#)
3. [Pacific physical activity guidelines for adults: framework for accelerating the communication of physical activity guidelines](#)

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of findings tables

Being overweight or obese

	Outcome	Odds Ratio (OR) (confidence intervals)	Mean difference (MD) (confidence intervals) <i>negative values favour intervention</i>
GRADE Table 1 (de Silva et al 2016 ; Mizuno et al 2014) Metformin vs. placebo	Change in weight (kg)	N/A	MD 3.24 lower (4.72 lower to 1.76 lower) LOW
	Change in weight - percentage of clinically relevant weight loss	OR 5.89 (1.81 to 19.16) LOW <i>values above 1 favour intervention</i>	N/A
	Mean BMI (kg/m2) or change in BMI	N/A	MD 1.11 lower (1.62 lower to 0.6 lower) LOW
	Maintenance of weight change / attenuation / prevention of weight gain - percentage of clinically relevant weight gain	OR 0.11 (0.03 to 0.41) VERY LOW <i>values below 1 favour intervention</i>	N/A
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	Narrative; results not pooled. No consistent results either in favour of against metformin. VERY LOW	
GRADE Table 2 (Mizuno et al 2014 ; Gierisch et al 2013)	Change in weight (kg)	N/A	MD 2.27 lower (4.76 lower to 0.23 higher) VERY LOW

Amantadine vs. placebo	Change in weight - percentage of clinically relevant weight loss	11.9% intervention group vs. 4.7% placebo group Statistical significance not reported. VERY LOW	
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain - percentage of clinically relevant weight gain	8.5% intervention group vs 9.4% placebo Statistical significance not reported. VERY LOW	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	1/12 in amantadine group withdrew due to significant worsening of psychosis. VERY LOW	
GRADE Table 3 (Mizuno et al 2014 ; Gierisch et al 2013) Aripiprazole vs. placebo	Change in weight (kg)	N/A	MD 2.13 lower (2.87 lower to 1.39 lower) LOW
	Change in weight - percentage of clinically relevant weight loss	15.0% intervention group vs. 3.0% placebo Statistical significance not reported. LOW	
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain - percentage of clinically relevant weight gain	1.9% intervention group vs. 2.0% placebo Statistical significance not reported. LOW	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	More adverse events reported in intervention group than placebo, but statistical significance of this was not reported. VERY LOW	
GRADE Table 4 (Mizuno et al 2014)	Change in weight (kg)	N/A	MD 0.75 higher (1.76 lower to 3.26 higher) VERY LOW

Fluoxetine vs. placebo	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain - percentage of clinically relevant weight gain	60.0% in both groups VERY LOW	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	
GRADE Table 5 (Mizuno et al 2014; Gierisch et al 2013) Nizatidine vs. placebo	Change in weight (kg)	N/A	MD 2.03 lower (4.53 lower to 0.47 higher) VERY LOW
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	2 in intervention group discontinued study, 1 in placebo group (n=54). Statistical significance not reported. VERY LOW	
GRADE Table 6 (Mizuno et al 2014) Orlistat vs. placebo	Change in weight (kg)	Mean change in kg was $-1.25 \pm \text{SD } 4.33$ in the intervention group, and $0.44 \pm \text{SD } 3.73$ in the placebo group. Statistical significance not reported. VERY LOW	
	Change in weight - percentage of clinically relevant weight loss	16.1% intervention group vs. 6.3% placebo Statistical significance not reported. VERY LOW	
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	

	Frequency of adverse events/side-effects	N/A	
GRADE Table 7 (Mizuno et al 2014) Reboxetine vs. placebo	Change in weight (kg)	N/A	MD 1.9 lower (3.07 lower to 0.72 lower) VERY LOW
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	OR 0.22 (0.08 to 0.60) VERY LOW <i>values below 1 favour intervention</i>	N/A
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	
GRADE Table 8 (Mizuno et al 2014) Rosiglitazone vs. placebo	Change in weight (kg)	N/A	MD 0.26 higher (1.83 lower to 2.35 higher) VERY LOW
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	
GRADE Table 9 (Mizuno et al 2014) Sibutramine vs. placebo	Change in weight (kg)	N/A	MD 2.86 lower (4.72 lower to 1.01 lower) VERY LOW
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	

	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	
GRADE Table 10 (Mizuno et al 2014) Topiramate vs. placebo	Change in weight (kg)	N/A	MD 5.2 lower (9.55 lower to 0.84 lower) VERY LOW
	Change in weight - percentage of clinically relevant weight loss	OR 7.76 (0.85 to 70.78) VERY LOW <i>values above 1 favour intervention</i>	N/A
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	
GRADE Table 11 (Gierisch et al 2013) Anti-psychotic switching from olanzapine vs. olanzapine	Change in weight (kg)	Switching to aripiprazole resulted in significantly more weight loss, but not switching to other anti-psychotics. VERY LOW	
	Mean BMI (kg/m2) or change in BMI	N/A	
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	Mixed results. VERY LOW	
GRADE Table 12 (Naslund et al 2017; Gierisch et al 2013)	Change in weight / Change in BMI	N/A	MD 0.2 lower (0.34 lower to 0.05 lower) VERY LOW

Short-term lifestyle interventions (6 months and under) vs. care as usual	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	Narrative; results not pooled. No significant differences found between groups. LOW	
GRADE Table 13 (Naslund et al 2017) Long-term lifestyle interventions (12 months and over) vs. care as usual	Change in weight / Change in BMI	N/A	MD 0.24 lower (0.36 lower to 0.12 lower) LOW
	Change in weight – achieving clinically significant (5% or greater) weight loss	OR 1.62 (1.21 to 2.16) LOW <i>values above 1 favour intervention</i>	N/A
	Maintenance of weight change / attenuation / prevention of weight gain	N/A	
	Reduced sedentary behaviour	N/A	
	Frequency of adverse events/side-effects	N/A	

At risk of becoming overweight or obese

	Outcome	Mean difference (MD) (confidence intervals) <i>negative values favour intervention</i>
GRADE Table 14 (Teasdale et al 2017) Lifestyle interventions vs. care as usual	Change in weight	MD 2.95 lower (4.38 lower to 1.52 lower) VERY LOW
	Mean BMI (kg/m2) or change in BMI	MD 0.95 lower (1.51 lower to 0.4 lower) VERY LOW
	Maintenance of weight change	N/A
	Attenuation/prevention of weight gain	N/A
	Reduced sedentary behavior	N/A
	Frequency of adverse events/side-effects	N/A

Evidence to Decision Table

	JUDGEMENT ⁵	EVIDENCE	ADDITIONAL CONSIDERATIONS							
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	• Persons with SMD are more likely to be obese (Compton et al., 2006). • Persons with SMD commonly have poor diets (Henderson et al., 2006). They consume more sugar and saturated fats than the general population (Dipasquale, et al., 2013), are less likely to exercise (Daumit et al., 2005), have a high prevalence of low physical activity (Stubbs et al 2017), and spend over 12 hours in sedentary activities on a daily basis (Janney et al, 2013). • This may be associated with higher rates of mortality and is related to other CVD risk outcomes. See Background section for further details.								
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?⁶ Weight management drugs <table><tr><td></td><td>Metformin</td><td>Amantadine</td><td>Nizatidine</td><td>Orlistat</td><td>Rosiglitazone</td><td>Sibutramine</td></tr></table>		Metformin	Amantadine	Nizatidine	Orlistat	Rosiglitazone	Sibutramine	In regards to the desirable anticipated effects, the evidence was as follows for the different interventions included in this review: Being overweight or obese • Metformin: Substantial effects in favour of metformin compared to placebo for change in weight (kg), percentage of clinically relevant weight loss, change in BMI, and percentage of clinically relevant weight gain, which were all statistically significant. Several other systematic reviews have also reported	The evidence and wording for ‘people with SMD who are at risk of becoming overweight/obese’ is unclear, as in the systematic review on prevention on weight gain (Teasdale et al 2017), in three of the four studies participants were already overweight. The PICO questions were therefore combined into one when formulating the recommendations.
	Metformin	Amantadine	Nizatidine	Orlistat	Rosiglitazone	Sibutramine				

⁵ These were made based on the available evidence and/or the GDG's expertise.

⁶ Please note that where interventions had already been excluded as possible recommendation, these were not considered further, and have therefore been shaded out.

Trivial						
Small						
Moderate						
Large						
Varies						
Don't know						

Anti-psychotics

	Aripiprazole	Fluoxetine	Reboxetine	Topiramate	Anti-psychotic switching
Trivial					
Small					
Moderate					
Large					
Varies					
Don't know					

Non-pharmacological interventions

	Short-term lifestyle interventions	Long-term lifestyle interventions
Trivial		

statistically significant effects in favour of metformin for both change in weight and BMI (Agarwal et al 2017, Gierisch et al 2013/2014, Liu et al 2015, Mizuno et al 2014, Siskind et al 2016).

- **Amantadine:** Effect in favour of amantadine compared to placebo for change in weight, though this was not statistically significant. Statistical significance not reported for other outcomes.
- **Aripiprazole:** Substantial and statistically significant effect in favour of aripiprazole compared to placebo for change in weight. Statistical significance not reported for other outcomes. Another systematic review (Agarwal et al 2017) also found a significantly greater reduction in weight in patients treated with aripiprazole (n = 236, 2 RCTs, MD -2.00 kg CI -2.96 to -1.03 kg); however, the authors noted that interpretation for this agent is limited by the small number of studies, small sample size, and short study duration.
- **Fluoxetine:** Small effect in favour of placebo for change in weight, which was not statistically significant. No difference between groups for maintenance of weight change / attenuation / prevention of weight gain. Other outcomes not reported.
- **Nizatidine:** Substantial effect in favour of nizatidine compared to placebo, which was not statistically significant. Other outcomes not reported. Another systematic review (Agarwal et al 2017) also reported a significantly greater reduction in weight in patients treated with nizatidine (n =113, 3 RCTs, MD -4.42 kg CI -8.10 to -0.73 kg) compared with placebo;

Small		
Moderate		
Large		
Varies		
Don't know		

however, the authors noted that interpretation for this agent is limited by the small number of studies, small sample size, and short study duration. Conversely, Gierisch et al (2013) did not find a statistically significant effect for nizatidine compared to placebo in terms of change in weight (MD -0.49 kg, 95% CI, -1.26 to 0.27, 4 RCTs).

- **Orlistat:** Trend in favour of orlistat compared to placebo for change in weight, but statistical significance was not reported. Other outcomes not reported.
- **Reboxetine:** Substantial and statistically significant effect in favour of reboxetine compared to placebo for both change in weight and maintenance of weight change / attenuation / prevention of weight gain. Other outcomes not reported.
- **Rosiglitazone:** Small effect in favour of placebo for change in weight, which was not statistically significant. Other outcomes not reported.
- **Sibutramine:** Substantial and statistically significant effect in favour of sibutramine compared to placebo for change in weight. Other outcomes not reported. Another systematic review (Agarwal et al 2017) reported a significantly greater reduction in weight in patients treated with sibutramine (n= 68, 4 RCTs, MD -5.42 kg CI -8.33 to -2.51 kg), and also significantly greater reduction in BMI in patients treated with sibutramine (n= 68, 4 RCTs, MD -1.09 kg/m² CI -1.88 to -0.30 kg/m²) compared with placebo; however, the authors noted that interpretation for this agent is limited by the small number of studies, small sample size, and short study duration.

	Topiramate: Substantial and statistically significant effect in favour of topiramate compared to placebo for change in weight. Substantial effect in favour of topiramate for change in weight (percentage of clinically relevant weight loss), but which was not statistically significant. Other outcomes not reported. Another systematic review (Agarwal et al 2017) also found a statistically significant effect in weight change for topiramate (200 mg but not 100 mg) (n =37, 1 RCT, MD -5.05 kg CI -7.67 to -2.43 kg), and also a significantly greater reduction in BMI (200 mg but not 100 mg) (n= 37, 1 RCT, MD -1.91 kg/m² CI -3.11 to -0.71 kg/m²) compared with placebo, and that topiramate prevented a change in BMI in patients started on antipsychotic treatment (n= 67, 1 RCT, MD -2.45 kg/m² CI -4.39 to -0.51 kg/m²); however, the authors noted that interpretation for this agent is limited by the small number of studies, small sample size, and short study duration. Anti-psychotic switching from olanzapine: Statistically significant effect in favour of switching to aripiprazole from olanzapine for change in weight, but no significant differences in change of weight when switching to either quetiapine or two different forms of olanzapine. Other outcomes not reported. Short-term lifestyle interventions: There was a small effect in favour of the intervention for change in weight / change in BMI, which was statistically significant. Another systematic review (Gierisch et al 2013/2014) also found a statistically significant effect on weight change in favour of the intervention. Long-term lifestyle interventions: There was a small effect in favour of the intervention for change in	
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		weight / change in BMI, and change in weight – achieving clinically significant (5% or greater) weight loss, which were both statistically significant. PICO 3.2 – at risk of becoming overweight or obese Lifestyle interventions: Substantial effect in favour of intervention for change in weight, and a moderate effect in favour of intervention for mean BMI / change in BMI, which were both statistically significant. Other outcomes not reported. However, even though the systematic review (Teasdale et al 2017) looked at prevention of weight gain, in three of the four included studies participants were already overweight (i.e. over 25 BMI on average). There was no evidence for reduced sedentary behaviour for any of the included interventions.																																				
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? Weight management drugs <table><tr><td></td><td>Metformin</td><td>Amantadine</td><td>Nizatidine</td><td>Orlistat</td><td>Rosiglitazone</td><td>Sibutramine</td></tr><tr><td>Trivial</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Small</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Moderate</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Large</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Metformin	Amantadine	Nizatidine	Orlistat	Rosiglitazone	Sibutramine	Trivial							Small							Moderate							Large							In regards to undesirable anticipated effects (frequency of adverse events/side-effects,) the evidence was as follows for the different interventions included in this review: PICO 3.1 – being overweight or obese Metformin: No consistent results either in favour of against metformin. Amantadine: Evidence not clear. Aripiprazole: More adverse events reported in intervention group than placebo, but statistical significance of this was not reported. Another systematic review (Agarwal et al 2017) also reported	
	Metformin	Amantadine	Nizatidine	Orlistat	Rosiglitazone	Sibutramine																																
Trivial																																						
Small																																						
Moderate																																						
Large																																						

Varies						
Don't know						

Anti-psychotics

	Aripiprazole	Fluoxetine	Reboxetine	Topiramate	Anti-psychotic switching
Trivial					
Small					
Moderate					
Large					
Varies					
Don't know					

Non-pharmacological interventions

	Short-term lifestyle interventions	Long-term lifestyle interventions
Trivial		
Small		
Moderate		
Large		
Varies		

that aripiprazole resulted in significantly higher occurrence of nausea and anxiety compared to placebo.

- **Fluoxetine:** No evidence available.
- **Nizatidine:** Evidence not clear based on grading. Another systematic review (Agarwal et al 2017) reported that nizatidine did not differ compared to placebo with respect to the frequency of adverse effects, and did not result in worsening of mental status or in higher dropout rates.
- **Orlistat:** No evidence available.
- **Reboxetine:** No graded evidence available. Another systematic review (Agarwal et al 2017) reported that reboxetine did not differ compared to placebo with respect to the frequency of adverse effects, and did not result in worsening of mental status or in higher dropout rates.
- **Rosiglitazone:** No evidence available.
- **Sibutramine:** No evidence available for grading. Another systematic review (Agarwal et al 2017) reported that sibutramine did not differ compared to placebo with respect to the frequency of adverse effects, and did not result in worsening of mental status or in higher dropout rates. However, sibutramine has been withdrawn in several countries due to cardiac risks.
- **Topiramate:** No evidence available for grading. However, Agarwal et al (2017) reported that topiramate did not differ compared to placebo with respect to the frequency of adverse effects, and did not result in worsening of mental status or in higher dropout rates, and may even be associated with improvement in clinical status.
- **Anti-psychotic switching from olanzapine:**

	Don't know	Evidence not clear. • Short-term lifestyle interventions: No significant differences found between groups for adverse events / side-effects. • Long-term lifestyle interventions: No evidence available. PICO 3.2 – at risk of becoming overweight or obese • Lifestyle interventions: No evidence available.	
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? X Very low to Low (see column to the right) ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence of effects was rated to be VERY LOW for all interventions, with a few exceptions: • Metformin: Change in weight and change in BMI were rated as LOW. • Aripiprazole: Change in weight and maintenance of weight change / attenuation / prevention of weight gain rated as LOW. • Short-term lifestyle interventions: Frequency of adverse events/side-effects rated as LOW. • Long-term lifestyle interventions: Change in weight / change in BMI, and change in weight – achieving clinically significant (5% or greater) weight loss were both rated as LOW.	
VALUES AND PREFERENCES	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or	The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012).	The GDG considered there to be indirect evidence that people with SMD value not gaining weight weight. Also see Yeisen et al (2017), which suggests that weight gain from anti-psychotics impacts on adherence.

	variability ○ Probably no important uncertainty or variability X No important uncertainty or variability		
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	The balance between desirable and undesirable effects varied for the different interventions included in this review: Being overweight or obese ● Metformin: Evidence from several systematic review (meta-analysis) in favour of metformin, though evidence on undesirable effects is not consistent. ● Amantadine: Insufficient evidence available to assess the balance between desirable and undesirable effects. ● Aripiprazole: Emerging evidence in favour of aripiprazole, though undesirable effects appear higher than for placebo, and results still need to be treated with caution. ● Fluoxetine: Insufficient evidence available to assess the balance between desirable and undesirable effects. ● Nizatidine: Evidence not sufficiently consistent to assess the balance between desirable and undesirable effects. ● Orlistat: Insufficient evidence available to assess the balance between desirable and undesirable effects. ● Reboxetine: Emerging evidence in favour of	

intervention							
Favors the intervention							
Varies							
Don't know							

reboxetine compared to placebo, though results still need to be treated with caution.

- **Rosiglitazone:** Insufficient evidence available to assess the balance between desirable and undesirable effects.
- **Sibutramine:** Some emerging evidence in favour of sibutramine compared to placebo, though results need to be treated with caution, and sibutramine has been withdrawn from use in several countries due to cardiac risks.
- **Topiramate:** Some emerging evidence in favour of topiramate compared to placebo, though results still need to be treated with caution.
- **Anti-psychotic switching from olanzapine:** Insufficient evidence available to assess the balance between desirable and undesirable effects, though there may be some emerging evidence in favour of switching to aripiprazole; results need to be treated with caution.
- **Short-term lifestyle interventions:** Evidence points to being in favour of the intervention compared to care as usual.
- **Long-term lifestyle interventions:** Insufficient evidence available to assess the balance between desirable and undesirable effects, as no data available for undesirable effects.

At risk of becoming overweight or obese

- **Lifestyle interventions:** Insufficient evidence available to assess the balance between desirable

		and undesirable effects, as no data available for undesirable effects.	
RESOURCES REQUIRED	How large are the resource requirements (costs)?	Of the pharmacological interventions included in this review, the following are included in the WHO Essential Medicines List (EML): • Metformin: Included in EML, as treatment for diabetes. • Amantadine: Not included in EML. • Aripiprazole: Not included in EML. • Fluoxetine: Included in EML, but as medication for palliative care and depressive disorders. • Nizatidine: Not included in EML, though another H2-receptor antagonist, ranitidine, is included. • Orlistat: Not included in EML. • Reboxetine: Not included in EML. • Rosiglitazone: Not included in EML. • Sibutramine: Not included in EML. • Topiramate: Not included in EML. The resource requirements for the pharmacological interventions is likely to be lower than for the non-pharmacological interventions (due to the elevated training and human resource costs associated with non-pharmacological interventions), though of the included	Adjunct aripiprazole is expensive.

		pharmacological interventions only metformin and fluoxetine are included in the WHO EML.																																											
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? <table><tr><td></td><td>Metformin</td><td>Aripiprazole</td><td>Reboxetine</td><td>Anti-psychotic switching</td><td>Short-term lifestyle interventions</td><td>Long-term lifestyle interventions</td></tr><tr><td>Very low</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Low</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Moderate</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>High</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>No included studies</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions	Very low							Low							Moderate							High							No included studies							No evidence identified.	Conclusions were made by expert consensus
	Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions																																							
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COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence identified.																																				
EQUITY	What would be the impact on health equity? <table><tr><td></td><td>Metformin</td><td>Aripiprazole</td><td>Reboxetine</td><td>Anti-psychotic switching</td><td>Short-term lifestyle interventions</td><td>Long-term lifestyle interventions</td></tr><tr><td>Reduced</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably reduced</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably no impact</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions	Reduced							Probably reduced							Probably no impact							Probably							No evidence identified.	Conclusions were made by expert consensus
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Increased																																																				
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Don't know																																																				
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? <table><tr><td></td><td>Metformin</td><td>Aripiprazole</td><td>Reboxetine</td><td>Anti-psychotic switching</td><td>Short-term lifestyle interventions</td><td>Long-term lifestyle interventions</td></tr><tr><td>No</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably no</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably yes</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Yes</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Varies</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Don't know</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions	No							Probably no							Probably yes							Yes							Varies							Don't know							No evidence identified.	Conclusions were made by expert consensus
	Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions																																														
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Probably yes																																																				
Yes																																																				
Varies																																																				
Don't know																																																				
FEASIBILITY	Is the intervention feasible to implement?	Studies for the different interventions have been conducted in the following countries: Being overweight or obese	Consider: - resources - programmatic interests																																																	

		Metformin	Aripiprazole	Reboxetine	Anti-psychotic switching	Short-term lifestyle interventions	Long-term lifestyle interventions	
No								
Probably no								
Probably yes								
Yes								
Varies								
Don't know								

- **Metformin:** China, Venezuela, Taiwan, Sri Lanka, Iran and USA
- **Amantadine:** USA only
- **Aripiprazole:** USA and Austria
- **Fluoxetine:** Israel and USA
- **Nizatidine:** Turkey and USA
- **Orlistat:** Finland
- **Reboxetine:** Israel
- **Rosiglitazone:** Venezuela and USA
- **Sibutramine:** Austria and USA
- **Topiramate:** South Korea and India
- **Anti-psychotic switching from olanzapine:** USA, Canada, Mexico and countries in Europe and elsewhere (unspecified).
- **Short-term lifestyle interventions:** USA, Spain, Taiwan, China, Thailand, countries in Asia (unspecified)
- **Long-term lifestyle interventions:** USA and UK

At risk of becoming overweight or obese

- **Lifestyle interventions:** Australia, Germany, Italy and Spain

See box for costs on which medications are included in the WHO EML.

For the non-pharmacological interventions, although intervention features, such as duration or frequency, could possibly be adapted for each particular setting, e.g.

- infrastructure
- training

		by being administered by suitably trained and supported non-specialists, there is no direct evidence available to support this. There were high drop-out rates for the non-pharmacological interventions.	
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WHO guidelines for general population

WHO Guidelines for primary health care in low-resource settings (2012):

- Tobacco use, unhealthy diet and physical inactivity: shared risk factor for NCD prevention/control priority conditions (CVD, diabetes, chronic respiratory disease and cancer)
- Advise overweight patients to reduce weight by reducing their food intake.
- Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

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Morgan VA, Waterreus A, Jablensky A, Mackinnon A, McGrath JJ, Carr V, Bush R, Castle D, Cohen M, Harvey C, Galletly C. People living with psychotic illness in 2010: the second Australian national survey of psychosis. *Australian & New Zealand Journal of Psychiatry*. 2012 Aug;46(8):735-52.

Stubbs B et al. Physical activity correlates among people with psychosis: Data from 47 low- and middle-income countries. *Schizophrenia Research*. 2017

Yeisen RAH et al. Experiences of antipsychotic use in patients with early psychosis: a two-year follow-up study. *BMC Psychiatry*. 2017; 17:299

GDG Recommendations

3 For people with SMD who are overweight or obese, or are at risk of becoming overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

RECOMMENDATIONS	Recommendations: Recommendation 1: Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with <i>WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)</i>. These interventions should be appropriate and tailored to the needs of this population. <i>(Strength of recommendation: Strong; Quality of evidence: Very low)</i>. The WHO guidance on overweight and obesity should be followed as per the “Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012)” (http://www.who.int/nmh/publications/phc2012/en/) - Advise overweight patients to reduce weight by following a balanced diet. - Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet. - Advise patients to reduce sedentary behaviour and practice regular daily physical activity appropriate for their physical capabilities (e.g. walking). ▪ Recommendation 2: For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring. <i>(Strength of recommendation: Conditional; Quality of evidence: Low)</i>.
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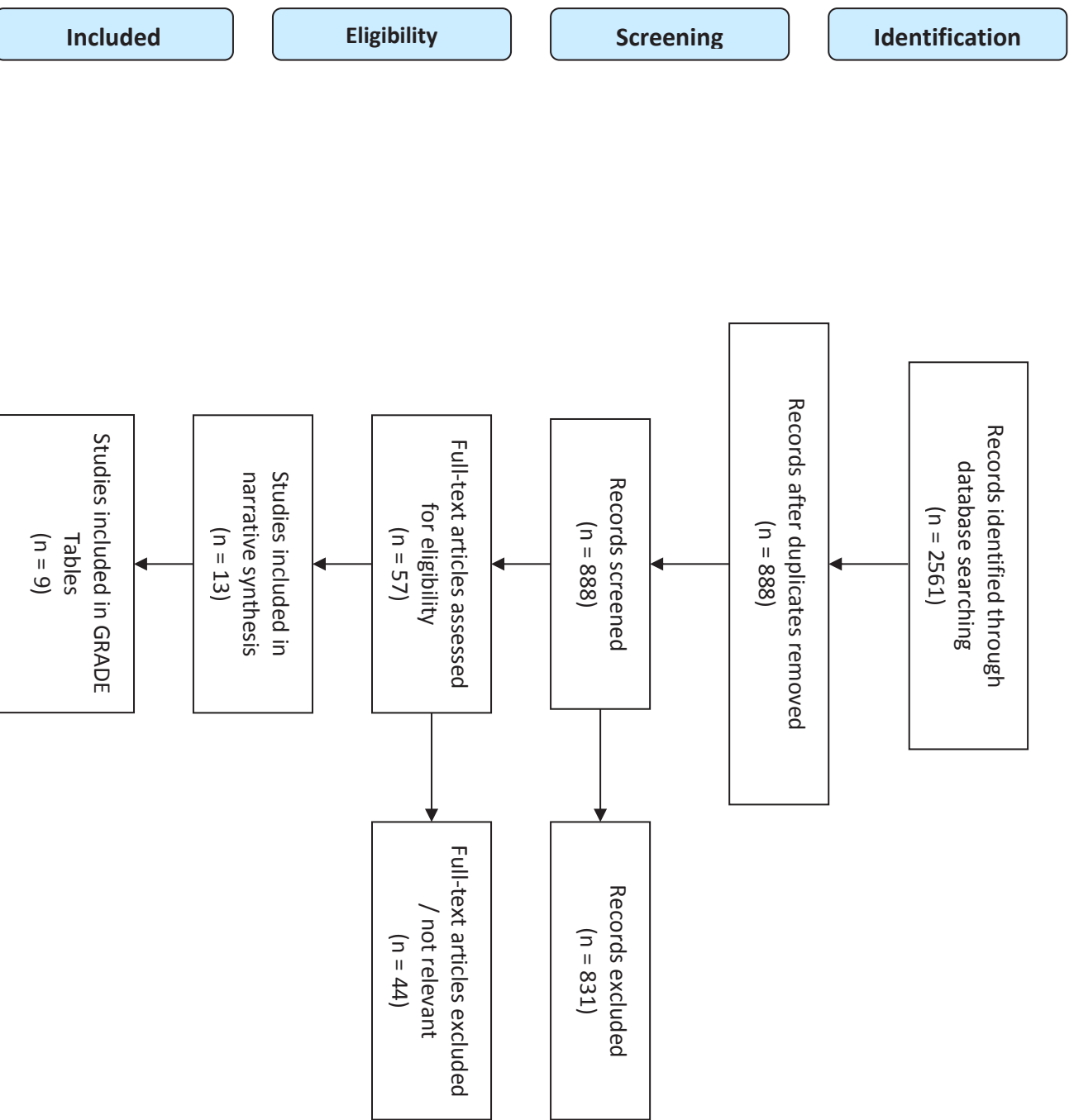
	Best practice statements: - For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects. - For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects. <u>Additional considerations:</u> ▪ Metformin is a commonly used anti-diabetic medication but it can be used for weight loss in people who are not diabetic. Metformin for people with SMD who are overweight or obese: ○ Should preferably be initiated in specialist settings, and should be closely monitored. ○ Should be tried in the short-term before being used in the long-term. ○ Availability may be an issue, i.e. metformin is not reliably available in all settings. ▪ Fluoxetine may increase the potency of metformin based on the drug-drug interaction searches (Annex 7). Monitor blood glucose control and adjust doses of metformin accordingly, especially when starting or stopping fluoxetine. Risperidone and clozapine are associated with hyperglycaemia and as such may decrease the efficacy of anti-diabetic medication including metformin. Monitor glycaemic control and adjust doses of anti-diabetic medications accordingly.
JUSTIFICATION	The GDG concluded that the behavioural lifestyle interventions recommended in the WHO guidelines for the general population should be followed in people with SMD since there is some evidence from the general population that advising people to give preference to low glycaemic index foods, follow a balanced diet and advice on exercise may have a beneficial effect on glycaemic control, although the evidence in the general population is of low quality, these simple interventions are deemed as low-cost, feasible and with a negligible risk of adverse events, and there is no high quality evidence to indicate that these interventions are ineffective in people with SMD. The GDG made a strong recommendation for non-pharmacological behavioural/lifestyle interventions, as they concluded that the benefits outweighed the harms including benefits of the intervention on other non-communicable disease outcomes. WHO general population guidelines (WHO PEN) also make a strong recommendation for these interventions in the general population. With regards to

	pharmacological interventions, the GDG made a strong recommendation for initiating a psychotropic medication with lower propensity for weight gain. The recommendation for switching antipsychotic medication was rated by the GDG as conditional since the quality of the evidence was low and switching antipsychotics because of weight gain should be offset against the risk of relapse of the mental disorder, as well as any potential side effects associated with the newly introduced medication.
SUBGROUP CONSIDERATIONS	No remarks.
IMPLEMENTATION CONSIDERATIONS	Relevant modules from the mhGAP guidelines for the management of mental disorders should be followed. Also refer to the relevant publications from the WHO¹ listed below. Most studies were conducted in well-resourced settings, however shorter-term behavioural interventions were assessed in a range of countries (USA, Spain, Taiwan, China, and Thailand), whilst longer-term behavioural interventions (>12 months or more) were assessed in the UK and USA only. Studies assessing metformin versus placebo in adults with schizophrenia and schizoaffective disorders prescribed antipsychotics have been conducted in a range of countries (including in China, Venezuela, Taiwan, Sri Lanka, Iran and the USA) and included diet/nutrition and/or exercise counselling in control and intervention groups.
MONITORING AND EVALUATION	No remarks.
RESEARCH PRIORITIES	Well conducted multi-site trials are needed on antipsychotic medication switching for weight gain, and maintenance of weight loss, in SMD. More high-quality studies, including randomized controlled trials, are needed from low- and middle-income countries. More research is needed on prevention of weight gain amongst people with SMD who are not already overweight when initiating anti-psychotic medication.

References

1. [Global recommendations on physical activity for health](#) ; [Interventions on diet and physical activity: what works: summary report](#) ; [Pacific physical activity guidelines for adults: framework for accelerating the communication of physical activity guidelines](#) ; WHO *Guidelines for primary health care in low-resource settings* (2012)
2. Taylor et al. *Maudsley Prescribing Guidelines* (2018, in press).
3. Cooper et al (2016) *BAP guidelines*
4. *NICE guidelines Psychosis and schizophrenia in adults: prevention and management* (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014)

**PRISMA Flow Diagram for systematic review of the reviews:
SMD and weight management**



EVIDENCE PROFILE

SUBSTANCE USE DISORDERS

PICO QUESTION: For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Background on the PICO question

There are high levels of comorbidity for SMD and substance use disorder. Having an SMD increases the risk of developing a substance use disorder (such as alcohol, cannabis or amphetamine abuse) (Schlossarek et al 2016), and vice versa (Marconi et al 2016).

For people with SMD, the following pooled prevalence rates of substance use disorder have been reported in systematic reviews: 8.9% amongst people with psychotic disorders (Sara et al 2015); 24-42% alcohol use, 20% cannabis use, 17% illicit drug use in people with bipolar disorder (Di Florio et al 2014; Hunt et al 2016a, b). Cannabis use/abuse/dependence in people with schizophrenia (or similar mental disorders such as schizoaffective or schizophreniform disorder) has been a particular focus on several research studies, which have reported prevalence rates of cannabis use in people with schizophrenia of between 5% and 69% (Hanna et al 2017; McLoughlin et al 2014). This may in part be because substance abuse is the most prevalent comorbid psychiatric condition associated with schizophrenia, and cannabis is the illicit drug most often abused (Malchow et al (2013).

For people with substance use (disorder), the risk of developing an SMD is also heightened (Jonsson et al 2014); for example Hunt et al (2016a) found that that people with an alcohol use disorder (AUD) were at 4.1 times of greater risk of having bipolar disorder compared to those without an AUD, and illicit drug users had 5.0 times the greater risk of having BD compared to non-users. Similarly, Lai al (2015) reported that people with comorbid illicit drug use disorder had a 3.8-fold risk of having major depression.

These risks may be variable in regards to geographical location, gender (men are at a higher lifetime risk of a substance use disorder than women), age of onset/substance use, genetic susceptibility, service setting and clinical differences (Andersen et al 2017; Di Florio et al 2014; Hunt et al 2016b; Malchow et al 2013; Messer et al 2017; Parack & Basu 2013; Sara et al 2015), and there may also be a dose-response relationship between level of substance use and risk of mental disorder (Jonsson et al 2014; Marconi et al 2016).

In addition, comorbid mental disorders amongst people with substance use disorder may also be an important risk factor for severe substance-use related outcomes; for example, depression has been found to be a significant predictor of non-fatal overdoses amongst people with substance use disorder (OR 1.45, CI: 1.17-1.79) (Bartoli et al 2014), and comorbid alcohol use disorder and bipolar disorder have been shown to be associated with an increased risk of suicide (pooled crude ORs of 1.96 (95% CI=1.56-2.47; $p<0.01$), and more so than for either AUD (1.72 (95% CI=1.52-1.95; $p<0.01$) or SUD alone (1.77 (95% CI=1.49-2.10; $p<0.01$) (Carra et al 2014). Similarly, continued cannabis use after onset of psychosis may predict adverse outcomes, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users (Schoeler et al 2016).

There have been several Cochrane systematic reviews conducted on interventions for people with substance use disorder (in the general population), which have provided evidence on the effectiveness of the following interventions:

- Psychosocial interventions, such as combined motivational enhancement therapy (MET) and CBT with abstinence-based incentives in cannabis use disorder (Gates et al 2016).
- Methadone in people with opioid dependence (Mattick et al 2014).

Conversely, evidence from Cochrane reviews has not found any – or inconsistent – evidence for the effectiveness of the following interventions to reduce substance use:

- Case management (though it did increase linkage with other services) for people with substance use disorder (Hesse et al 2014)
- Anti-psychotic medications for treatment of cocaine dependence (Indave et al 2016), though there has been an indication that second-generation antipsychotics such as Risperidone may result in improved outcomes in the treatment of dual diagnosis (Temmingh et al 2018).
- No evidence for effectiveness of SSRI antidepressants, mixed action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone), norepinephrine reuptake inhibitors (atomoxetine) for treatment of cannabis dependence. THC preparations and anticonvulsant gabapentin and the glutamatergic modulator N-acetylcysteine are worth exploring for cannabis dependence (Marshall et al 2014).

This document covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD and substance use disorder. Those outcomes were included, which were considered to be critical substance use disorder related outcomes.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Population: people with SMD and substance (drug and/or alcohol) use disorder

Intervention:

pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions: e.g. motivational interviewing and/or CBT, psychoeducation, brief assessment interview, dual-focus interventions

Comparison: care as usual / placebo or one treatment vs another

Outcomes:

Critical

- Level of consumption
- Frequency of use
- Abstinence
- Relapse rates

Important:

- Frequency of adverse events / side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Agabio et al. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. Cochrane Database of Systematic Reviews. 2018; 4: CD008581

Boniface S et al. The effect of brief interventions for alcohol among people with comorbid mental health conditions: A systematic review of randomized trials and narrative synthesis. *Alcohol and Alcoholism*. 2018; 53(3): 282-293

Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. *Cochrane Database of Systematic Reviews*. 2013; 10(10): CD001088
(also see Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. *Schizophr Bull*. 2014; 40(1): 18-20: Brief overview paper of this Cochrane review)

Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. *Cochrane Database of Systematic Reviews*. 2018; 1

Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. *J Psychopharmacol*. 2016; 13(2): 99-111

EXCLUDED FROM GRADE TABLES

Abayomi, O & Adelufosi, AO. Psychosocial interventions for cannabis abuse and/or dependence among persons with co-occurring cannabis use and psychotic disorders. *Cochrane Database of Systematic Reviews*. 2015; 1 (protocol)

Adida M et al. Co-occurring mood and substance use disorders. *Encephale*. 2014; 40(S3): S8-S13

Alvarez Y et al. Antipsychotic drugs in cocaine dependence: a systematic review and meta-analysis. *Journal of Substance Abuse Treatment*. 2013; 45(1): 1-10

Arranz B et al. Clozapine use in patients with schizophrenia and a comorbid substance use disorder: A systematic review. *European Neuropsychopharmacology*. 2017

Azorin JM et al. Pharmacological treatment of schizophrenia with comorbid substance use disorder. *Expert Opin Pharmacother*. 2016; 17(2): 231-253

Babowitch JD & Antshel KM. Adolescent treatment outcomes for comorbid depression and substance misuse: A systematic review and synthesis of the literature. *Journal of Affective Disorders*. 2016; 201: 25-33

Bennett ME, Bradshaw KR, Catalano LT. Treatment of substance use disorders in schizophrenia. *The American Journal of Drug and Alcohol and Abuse*. 2017; 43(4):377-390

Boyuan Z et al. Efficacy of acupuncture for psychological symptoms associated with opioid addiction: a systematic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine*. 2014

- Chow CM et al. Mission impossible: Treating serious mental illness and substance use co-occurring disorder with integrated treatment: A meta-analysis. *Mental Health and Substance Use*. 2013; 6(2): 150-168
- Cooper SJ et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol*. 2016; 30(8): 717-48
- Crockford D & Addington D. Canadian Schizophrenia Guidelines: Schizophrenia and Other Psychotic Disorders with Coexisting Substance Use Disorders. *Canadian Journal of Psychiatry*. 2017; 62(9): 624-634
- De Witte N et al. Treatment for outpatients with comorbid schizophrenia and substance use disorders: a review. *Eur Addict Res*. 2014;20(3):105-14
- Foulds JA et al. Depression in patients with alcohol use disorders: Systematic review and meta-analysis of outcomes for independent and substance-induced disorders. *Journal of Affective Disorders*. 2015; 185: 47-59
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- Helton SG & Lohoff FW. Pharmacogenetics of alcohol use disorders and comorbid psychiatric disorders. *Psychiatry Res*. 2015; 230(2): 121-129
- Hjorthoj CR et al. Intervention efficacy in trials targeting cannabis use disorders in patients with comorbid psychosis systematic review and meta-analysis. *Curr Pharm Des*. 2014; 20(13): 2205-2211
- Hobden B et al. Finding the optimal treatment model: A systematic review of treatment for co-occurring alcohol misuse and depression. *Australian & New Zealand Journal of Psychiatry*. 2018; 52(8): 737-750
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(also see Pushpa-Rajah JA et al. Cannabis and schizophrenia. *Schizophrenia Bulletin*. 2015; 41(2): Brief overview paper of this Cochrane review)
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- Perry AE et al. Interventions for drug-using offenders with co-occurring mental illness. Cochrane Database of Systematic Reviews. 2015; 6
- Peters RH et al. Evidence-based treatment and supervision practices for co-occurring mental and substance use disorders in the criminal justice system. The American Journal of Drug and Alcohol Abuse. 2017; 43(3): 475-488
- Preuss UW et al. Psychische komorbiditäten bei alkoholbedingten Störungen. Der Nervenarzt. 2016; 87(1): 26-34
- Riper et al. Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: a meta-analysis. Addiction. 2014; 109(3): 394-406
- Sabioni P et al. The effectiveness of treatments for cocaine dependence in schizophrenic patients: a systematic review. Current neuropharmacology. 2013; 11(5): 484-490
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- Secades-Alvares A & Fernandez-Rodriguez C. Review of the efficacy of treatments for bipolar disorder and substance abuse. Revista de Psiquiatria y Salud Mental. 2017; 10(2): 113-124
- Spijker AT et al. Bipolaire stoornissen en alcoholafhankelijkheid; praktische aanbevelingen voor behandeling op basis van een systematische literatuurstudie: Tijdschrift Voor Psychiatrie 60(2018)2, 87-95
- Timko C et al. Screening and brief intervention for unhealthy substance use in patients with chronic medical conditions: a systematic review. J Clin Nurs. 2016; 25 (21-22): 3131-3143
- Woodhouse R et al. Interventions for drug-using offenders with co-occurring mental health problems: a systematic review and economic appraisal. Health & justice. 2016; 4(1): 10
- Zhou X et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: a systematic review and meta-analysis. Addiction. 2014; 110: 38-48

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Risperidone vs. olanzapine	level of consumption	Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	Most recent high-quality (Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
		frequency of use	No relevant systematic review available.	N/A
		abstinence	Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	Most recent high-quality (Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	Most recent high-quality (Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
2	Risperidone vs. clozapine	level of consumption	No relevant systematic review available.	N/A
		frequency of use	Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	Most recent high-quality (Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
		abstinence	Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	Most recent high-quality (Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse	Temmingh HS et al. Risperidone versus other	Most recent high-quality

		events / side-effects	antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1	(Cochrane) systematic review (meta-analysis) for people with SMD and substance abuse.
3	Ziprasidone vs. clozapine	level of consumption	Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111	Most recent high-quality systematic review, though for people with psychosis and cannabis misuse.
		frequency of use	No relevant systematic review available.	N/A
		abstinence	No relevant systematic review available.	N/A
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111	Most recent high-quality systematic review, though for people with psychosis and cannabis misuse.
4	Clozapine vs. care as usual	level of consumption	Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111	Most recent high-quality systematic review, though for people with psychosis and cannabis misuse.
		frequency of use	No relevant systematic review available.	N/A
		abstinence	No relevant systematic review available.	N/A
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111	Most recent high-quality systematic review, though for people with psychosis and cannabis misuse.
		frequency of use		
		abstinence		
		relapse rates		
		frequency of adverse		

		events / side-effects		
5	Cognitive behaviour therapy (CBT) plus motivational interviewing vs. care as usual	level of consumption	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		frequency of use	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		abstinence	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
6	Cognitive behaviour treatment vs. care as usual	level of consumption	No relevant systematic review available.	N/A
		frequency of use	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		abstinence	Hunt GE et al. Psychosocial interventions for	Most recent high-quality

			people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	(Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	No relevant systematic review available.	N/A
7	Motivational interviewing vs. care as usual	level of consumption	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		frequency of use	No relevant systematic review available.	N/A
		abstinence	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
8	Contingency management vs. care as usual	level of consumption	No relevant systematic review available.	N/A
		frequency of use	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people

				with SMD and substance abuse.
		abstinence	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
		relapse rates	No relevant systematic review available.	N/A
		frequency of adverse events / side-effects	Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088	Most recent high-quality (Cochrane) systematic review available on non-pharmacological interventions for people with SMD and substance abuse.
9	Brief motivational interviewing vs. educational treatment (ET)	level of consumption	Boniface S et al. The effect of brief interventions for alcohol among people with comorbid mental health conditions: A systematic review of randomized trials and narrative synthesis. Alcohol and Alcoholism. 2018; 53(3): 282-293	Most recent high-quality systematic review available on brief motivational interviewing vs. educational treatment for people with SMD and alcohol misuse.
		frequency of use		
		abstinence		
		relapse rates	No relevant systematic review available.	
		frequency of adverse events / side-effects		
10	Brief interventions vs. care as usual	level of consumption	Boniface S et al. The effect of brief interventions for alcohol among people with comorbid mental health conditions: A systematic review of randomized trials and narrative synthesis. Alcohol and Alcoholism. 2018; 53(3): 282-293	Most recent high-quality systematic review available on brief interventions vs. care as usual for people with SMD and alcohol misuse.
		frequency of use		
		abstinence	No relevant systematic review available.	
		relapse rates		
		frequency of adverse events / side-effects		
		11		

	placebo	frequency of use	people with co-occurring depression and alcohol dependence. Cochrane Database of Systematic Reviews. 2018; 4: CD008581	(Cochrane) systematic review on antidepressants for people with depression and comorbid alcohol dependence.
		abstinence		
		relapse rates		
		frequency of adverse events / side-effects		

Narrative description of the studies that went into analysis¹

Hunt et al (2013) conducted a Cochrane review, to assess the effects of psychosocial interventions for reduction in substance use in people with a serious mental illness compared with standard care. MAIN RESULTS: 32 trials were included with a total of 3165 participants. Evaluation of long-term integrated care included four RCTs (n = 735). No significant differences were found on loss to treatment (n = 603, 3 RCTs, RR 1.09 CI 0.82 to 1.45, low quality of evidence), death by 3 years (n = 421, 2 RCTs, RR 1.18 CI 0.39 to 3.57, low quality of evidence), alcohol use (not in remission at 36 months) (n = 143, 1 RCT, RR 1.15 CI 0.84 to 1.56, low quality of evidence), substance use (n = 85, 1 RCT, RR 0.89 CI 0.63 to 1.25, low quality of evidence), global assessment of functioning (n = 171, 1 RCT, MD 0.7 CI 2.07 to 3.47, low quality of evidence), or general life satisfaction (n = 372, 2 RCTs, MD 0.02 higher CI 0.28 to 0.32, moderate quality of evidence). For evaluation of non-integrated intensive case management with usual treatment (4 RCTs, n = 163) no statistically significant difference was found for loss to treatment at 12 months (n = 134, 3 RCTs, RR 1.21 CI 0.73 to 1.99, very low quality of evidence). Motivational interviewing plus cognitive behavioural therapy compared to usual treatment (7 RCTs, total n = 878) did not reveal any advantage for retaining participants at 12 months (n = 327, 1 RCT, RR 0.99 CI 0.62 to 1.59, low quality of evidence) or for death (n = 493, 3 RCTs, RR 0.72 CI 0.22 to 2.41, low quality of evidence), and no benefit for reducing substance use (n = 119, 1 RCT, MD 0.19 CI -0.22 to 0.6, low quality of evidence), relapse (n = 36, 1 RCT, RR 0.5 CI 0.24 to 1.04, very low quality of evidence) or global functioning (n = 445, 4 RCTs, MD 1.24 CI 1.86 to 4.34, very low quality of evidence). Cognitive behavioural therapy alone compared with usual treatment (2 RCTs, n = 152) showed no significant difference for losses from treatment at 3 months (n = 152, 2 RCTs, RR 1.12 CI 0.44 to 2.86, low quality of evidence). No benefits were observed on measures of lessening cannabis use at 6 months (n = 47, 1 RCT, RR 1.30 CI 0.79 to 2.15, very low quality of evidence) or mental state (n = 105, 1 RCT, Brief Psychiatric Rating Scale MD 0.52 CI -0.78 to 1.82, low quality of evidence). No advantage was found for motivational interviewing alone compared with usual treatment (8 RCTs, n = 509) in reducing losses to treatment at 6 months (n = 62, 1 RCT, RR 1.71 CI 0.63 to 4.64, very low quality of evidence), although significantly more participants in the motivational interviewing group reported for their first aftercare appointment (n = 93, 1 RCT, RR 0.69 CI 0.53 to 0.9). Some differences, favouring treatment, were observed in abstaining from alcohol (n = 28, 1 RCT, RR 0.36 CI 0.17 to 0.75, very low quality of evidence) but not other substances (n = 89, 1 RCT, RR -0.07 CI -0.56 to 0.42, very low quality of evidence), and no differences were observed in mental state (n = 30, 1 RCT, MD 0.19 CI -0.59 to 0.21, very low quality of evidence). We found no significant differences for skills training in the numbers lost to treatment by 12 months (n = 94, 2 RCTs, RR 0.70 CI 0.44 to 1.1, very low quality of evidence). We found no differences for contingency management compared with usual treatment (2 RCTs, n = 206) in numbers lost to treatment at 3 months (n = 176, 1 RCT, RR 1.65 CI 1.18 to 2.31, low quality of evidence), number of stimulant positive urine tests at 6 months (n = 176, 1 RCT, RR 0.83 CI 0.65 to 1.06, low quality of evidence) or hospitalisations (n = 176, 1 RCT, RR 0.21 CI 0.05 to 0.93, low quality of evidence). Findings could not be summarised due to skewed data or because trials did not measure the outcome of interest. In general, evidence was rated as low or very low due to high or unclear risks of bias because of poor trial methods, or poorly reported methods, and imprecision due to small sample sizes, low event rates and wide confidence intervals. AUTHORS' CONCLUSIONS: No compelling evidence was found to support any one psychosocial treatment over another for people to remain in treatment or to reduce substance use or improve mental state in people with serious mental illnesses. Furthermore, methodological difficulties exist which hinder pooling and interpreting results. Further high quality trials are required which address these concerns and improve the evidence in this important area.

¹ Please note that this section includes the abstracts as taken directly from the publications.

Temmingh et al (2018) conducted a Cochrane review, to evaluate the effects of risperidone compared to treatment with other antipsychotics (first-generation and other second-generation antipsychotics) used in people with serious mental illness and co-occurring substance misuse. Main results: Eight randomised trials containing a total of 1073 participants with SMI and co-occurring substance misuse were identified, of which seven contributed useable data to the review. There was heterogeneity in trial design and measurement. Risperidone was compared to clozapine, olanzapine, perphenazine, quetiapine and ziprasidone. Few trials compared risperidone with first-generation agents. Few trials examined participants with a dual diagnosis from the outset and most trials only contained separate analyses of subgroups with a dual diagnosis or were secondary data analyses of subgroups of people with a dual diagnosis from existing larger trials. For risperidone versus clozapine, no clear differences were found between these two antipsychotics in the reduction of positive psychotic symptoms (1 randomised controlled trial (RCT), $n = 36$, mean difference (MD) 0.90, 95% CI 2.21 to 4.01, very low quality evidence), or reduction in cannabis use (1 RCT, $n = 14$, risk ratio (RR) 1.00, 95% CI 0.30 to 3.35, very low quality evidence), improvement in subjective well-being (1 RCT, $n = 36$, MD = 6.00, 95% CI 14.82 to 2.82, very low quality evidence), numbers discontinuing medication (1 RCT, $n = 36$, RR 4.05, 95% CI 0.21 to 78.76, very low quality evidence), extrapyramidal side-effects (2 RCTs, $n = 50$, RR 2.71, 95% CI 0.30 to 24.08; $I^2 = 0\%$, very low quality evidence), or leaving the study early (2 RCTs, $n = 45$, RR 0.49, 95% CI 0.10 to 2.51; $I^2 = 34\%$, very low quality evidence). Clozapine was associated with lower levels of craving for cannabis (1 RCT, $n = 28$, MD 7.00, 95% CI 2.37 to 11.63, very low quality evidence). For risperidone versus olanzapine no clear differences were found in the reduction of positive psychotic symptoms (1 RCT, $n = 37$, MD = 1.50, 95% CI 3.82 to 0.82, very low quality evidence), reduction in cannabis use (1 RCT, $n = 41$, MD 0.40, 95% CI 4.72 to 5.52, very low quality evidence), craving for cannabis (1 RCT, $n = 41$, MD 5.00, 95% CI 4.86 to 14.86, very low quality evidence), parkinsonism (1 RCT, $n = 16$, MD 0.08, 95% CI 1.21 to 1.05, very low quality evidence), or leaving the study early (2 RCT, $n = 77$, RR 0.68, 95% CI 0.34 to 1.35; $I^2 = 0\%$, very low quality evidence). For risperidone versus perphenazine, no clear differences were found in the number of participants leaving the study early (1 RCT, $n = 281$, RR 1.05, 95% CI 0.92 to 1.20, low-quality evidence). For risperidone versus quetiapine, no clear differences were found in the number of participants leaving the study early (1 RCT, $n = 294$, RR 0.96, 95% CI 0.86 to 1.07, low-quality evidence). For risperidone versus ziprasidone, no clear differences were found in the number of participants leaving the study early (1 RCT, $n = 240$, RR 0.96, 95% CI 0.85 to 1.10, low-quality evidence). For many comparisons, important outcomes were missing; and no data were reported in any study for metabolic disturbances, global impression of illness severity, quality of life or mortality. Authors' conclusions: There is not sufficient good-quality evidence available to determine the effects of risperidone compared with other antipsychotics in people with a dual diagnosis. Few trials compared risperidone with first-generation agents, leading to limited applicability to settings where access to second-generation agents is limited, such as in low- and middle-income countries. Moreover, heterogeneity in trial design and measurement of outcomes precluded the use of many trials in the analyses. Future trials in this area need to be sufficiently powered but also need to conform to consistent methods in study population selection, use of measurement scales, definition of outcomes, and measures to counter risk of bias. Investigators should adhere to CONSORT guidelines in the reporting of results.

Wilson & Bhattacharyya (2016) conducted a systematic review, to evaluate evidence of antipsychotic efficacy in reducing the burden of psychotic symptoms and cannabis use in individuals with psychotic mental illness and co-morbid cannabis use. A systematic review was conducted of antipsychotic treatment in those with psychotic mental illness and co-morbid cannabis use. Quality of evidence for each study and outcomes were rated using the 'GRADE' approach. Twenty-two studies were identified: 13 experimental and 9 observational, including a total sample of 1543 patients, 761 of whom had a diagnosed cannabis use disorder. The most frequent antipsychotics compared were risperidone, olanzapine and clozapine with

olanzapine, risperidone and haloperidol. No clear differences between antipsychotics were demonstrated. The authors concluded that future studies are needed to confirm whether clozapine is superior to other antipsychotics in reducing cannabis use.

GRADE Evidence Tables²

Table 1: Risperidone vs. olanzapine for people with SMD and substance use disorder

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Risperidone compared to olanzapine for people with SMD and substance use disorder

Setting: inpatients and outpatients

Bibliography:

Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	risperidone	olanzapine	Relative (95% CI)	Absolute (95% CI)		
level of consumption - reduction of joints smoked per week (MD above 0 favours risperidone) (follow up: 6 weeks)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^c	publication bias strongly suspected ^d	21	20	-	MD 0.4 higher (4.72 lower to 5.52 higher)	⊕○○○ VERY LOW	CRITICAL
frequency of use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
abstinence - stopping cannabis use (RR above 1 favours risperidone) (follow up: 4 months)												

² See Annex 5, page XX for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	risperidone	olanzapine	Relative (95% CI)	Absolute (95% CI)		
1 ^e	randomised trials	not serious ^f	not serious	not serious	very serious ^g	none detected ^h	-/21	-/28	RR 1.19 (0.68 to 2.08)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
abstinence - stopping alcohol use (RR above 1 favours risperidone) (follow up: 4 months)												
1 ^e	randomised trials	not serious ^f	not serious	not serious	very serious ^g	none detected ^h	-/21	-/28	RR 1.31 (0.73 to 2.36)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - Parkinsonism (MD below 0 favours risperidone) (follow up: 14 weeks)												
1 ⁱ	randomised trials	very serious ^j	not serious	not serious	very serious ^k	none detected ^l	14	14	-	MD 0.08 lower (1.21 lower to 1.05 higher) ^m	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Only 1 study in Temmingh et al (2018) was included for this outcome. The study was conducted in the Netherlands with participants who had been diagnosed with schizophreniform, schizophrenia or schizoaffective disorder, of which a subgroup used cannabis (only these participants were included in the analysis in Temmingh et al 2018).

b. This has been rated as very serious, as there was an unclear risk of bias for masking of outcome assessment, unclear allocation concealment, possible unblinding through different side effect profiles of the two medications (this information was taken from the 'characteristics of included studies' table in Temmingh et al 2018), and the study had high drop-out rates (this information was taken from the individual study paper).

- c. This has been rated as very serious, as the number of participants is very low and the confidence intervals include both 'no effect', and appreciable benefit and harm.
- d. This has been rated as serious, as the authors of the systematic review (Temmingh et al 2018) reported that not all outcomes mentioned in the study protocol were included in the final study paper. Funnel plots could not be produced by the authors of the systematic review. Also, this was a pharma sponsored study.
- e. There was only 1 study in Temmingh et al 2018 that was included for this outcome. The study was conducted in the USA with participants who had been diagnosed with schizophrenia, schizophreniform or schizoaffective disorder, and a sub-sample of participant with comorbid cannabis use or dependence (only this group was included in the analyses). All participants also received psychoeducation about schizophrenia, were seen regularly by social workers, and had access to ancillary treatment service.
- f. This has been rated as not serious, as outcome assessment was masked, and drop-out rates were below 30% and similar across both groups (25%). See 'characteristics of included studies' table in Temmingh et al 2018.
- g. This has been rated as very serious, as the number of participants was very low, and the confidence intervals included both 'no effect' and appreciable benefit.
- h. No publication bias was detected, though funnel plots were not produced by the authors of the systematic review (Temmingh et al 2018). Some of the authors declared shares in pharma or receiving grant support from pharma and other competing interests; unclear whether this could have had an impact on the results, as the parent study was supported by NIH grants.
- i. Only 1 study was included for this outcome in Temmingh et al 2018. The study was conducted in the USA with participants who had a diagnosis of schizophrenia or schizoaffective disorder, and either cannabis or cocaine abuse or dependence. All participants also received weekly psychotherapy and were asked to nominate a 'significant other' to assist with attendance and follow-up.
- j. This has been rated as very serious, as the study had high and differential drop-out rates in the two groups (57% in olanzapine group, 29% in risperidone group). There was also an unclear risk of bias for masking of outcome assessment, and selective reporting of outcomes and for allocation concealment. This information was taken from 'characteristics of included studies' table in Temmingh et al 2018.
- k. This has been rated as very serious, as the number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.
- l. Publication bias was not detected, though funnel plots were not produced by the authors of the systematic review (Temmingh et al 2018) The study received support from Pharma.
- m. The other adverse event that was assessed in the study was weight gain, which was also not significant between groups (MD -1.0, -3.99-1.99). There were also no significant differences in leaving the study early between the two groups. This information was taken from page 76 in Temmingh et al 2018.

Table 2: Risperidone vs. clozapine for people with SMD and substance use disorder

Author(s): Maya Semrau (first rated), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Risperidone compared to clozapine for people with SMD and substance use disorder

Setting: inpatients and outpatients

Bibliography:

Temmingh HS et al. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews. 2018; 1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	risperidone	clozapine	Relative (95% CI)	Absolute (95% CI)		
level of consumption - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of use (RR above 1 favours risperidone) (follow up: 24 weeks)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^c	publication bias strongly suspected ^d	3/7 (42.9%)	3/7 (42.9%)	RR 1.00 (0.30 to 3.35)	0 fewer per 1,000 (from 300 fewer to 1,000 more)	⊕○○○ VERY LOW	CRITICAL
abstinence (RR above 1 favours risperidone) (follow up: 4 weeks)												
1 ^e	randomised trials	very serious ^f	not serious	not serious	very serious ^c	none detected ^g	-/16	-/12	RR 1.13 (0.41 to 3.12)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
relapse rates – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - any extrapyramidal (RR below 1 favours risperidone) ^h												
2 ⁱ	randomised trials	very serious ^j	not serious ^k	not serious	very serious ^l	publication bias strongly suspected ^m	-/23	-/22	RR 2.71 (0.30 to 24.08) ⁿ	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Only 1 study found in Temmingh et al (2018) reported on this outcome, measured by the Timeline-Follow-Back method; number of days cannabis used per week was rated as either improved (if 20% better), worse (if 20% worse), or unchanged (less than 20% change). The study was conducted in

the USA over 24 weeks with people who had schizophrenia or schizoaffective disorder and current cannabis abuse or dependence. All participants also received a lifestyle intervention to manage side-effects and to assist with recovery (cited in Temmingh et al, 2018).

b. This has been rated as very serious, as there was high drop-out rates in the study (about half of participants in the clozapine group, and 2 in the risperidone group, partly due to inability to tolerate medication side-effects); the masking of outcome assessment was also rated as an unclear risk Temmingh et al 2018 (see 'characteristics of studies' tables).

c. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit.

d. Publication bias was not assessed through funnel plots by the authors of the systematic review (Temmingh et al 2018), as only one study was included for this outcome. However, Temmingh et al (2018) considered the included study to have a high risk of bias for selective reporting (reporting bias) (see 'characteristics of included studies' table). Also, there are possible links with pharma, though these are unclear- study sponsorship independent of industry but authors may have had pharma links.

e. Only 1 study found in Temmingh et al (2018) reported on this outcome measured by the number of participants discontinuing cannabis. The study was conducted in the Netherlands over 4 weeks with people who had schizophrenia, schizoaffective or schizophreniform disorder, and cannabis use disorder. All participants also received 'supportive treatment as usual' (cited in Temmingh et al, 2018).

f. This has been rated as very serious, as this was an open label study, the outcome assessment was not masked, and there was differential drop-out rates in the two arms (20% in clozapine group, 0% in risperidone group). This information was taken from 'characteristics of studies' table in Temmingh et al (2018).

g. Publication bias was not assessed through funnel plots by the authors of the systematic review (Temmingh et al 2018).

h. Many adverse effects / side-effects were reported by the 2 included studies, though none of them were designated clinically important by the authors of the studies. 'Any extrapyramidal adverse effects' was used as a proxy in Temmingh et al (2018), so is included here.

i. The 2 studies were conducted in the USA and the Netherlands respectively. (cited in Temmingh et al 2018). See footnotes a and e above for details on these studies.

j. This has been rated as very serious, as there was a high risk of bias for masking of outcome assessment in 1 study and an unclear risk of bias for this in the other study, and there were high drop-out rates in 1 study and differential drop-out rates in the other study. This information was taken from Temmingh et al 2018.

k. This was rated as not serious, as heterogeneity (I^2) was reported to be 0% by Temmingh et al 2018 (see page 29).

l. This has been rated as very serious, as the number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.

m. Reporting bias was strongly suspected in one of the studies. This information was taken from 'characteristics of included studies' tables in Temmingh et al 2018.

n. Of the other 20 adverse effects analysed as well as the number of participants leaving the study early (due to any reason), none were statistically significant between the two groups. No participant left the study early due to inefficacy. See page 74 in Temmingh et al 2018.

Table 3: Ziprasidone vs. clozapine for people with SMD and substance use disorder

Author(s): Maya Semrau (first rated), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Ziprasidone compared to clozapine for people with SMD and substance use disorder

Setting: inpatients

Bibliography: Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	ziprasidone	clozapine	Relative (95% CI)	Absolute (95% CI)		
level of consumption - number of joints per month (follow up: 12 months)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^c	publication bias strongly suspected ^d	Baseline: Ziprasidone group: n=16, clozapine group: n=14. 12-month follow-up: ziprasidone group: n=7, clozapine group: n=5. Number of joints per month was significantly reduced to around 0 in both groups, with comparable findings between the two groups, and comparable findings at 3-month, 6-month and 12-month follow-up (i.e. level of consumption was around 0 in both groups at all three follow-up points). Main effect of group: F = 2.75; p = 0.128); interaction time x treatment (F = 2.14; p = 0.174). ^e				⊕○○○ VERY LOW	CRITICAL
frequency of use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
abstinence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^f	publication bias strongly suspected ^d	See above (level of consumption) for number of participants. There was a significant between-group effect on side-effects not favoring the clozapine group (F = 8.2; p = 0.017), which the authors (Schnell et al 2014) reported to be primarily due to hypersalivation.				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

- a. Wilson & Bhattacharyya (2016) only identified 1 study that reported on this outcome. The study was conducted in Germany, and included participants with schizophrenia, schizophreniform or schizoaffective disorder, as well as cannabis abuse or dependence. During follow-up after discharge from the hospital, all participants were also offered integrated treatment for the SMD/SUD.
- b. This has been rated as very serious, as the drop-out rate was very high (60%). This information was taken from the individual study paper.
- c. This has been rated as very serious, as the number of participants was very low, and there were no significant differences between treatment groups.
- d. Funnel plots were not produced by the authors of the systematic review (Wilson & Bhattacharyya (2016)) Also, the study was supported by Pfizer (cited in Wilson & Bhattacharyya (2016)).
- e. This information was taken from Wilson & Bhattacharyya (2016), table 3, and the individual study paper.
- f. This has been rated as very serious, as the number of participants is very low.

Table 4: Clozapine vs. care as usual for people with SMD and substance use disorder

Author(s): Maya Semrau (first rated), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Clozapine compared to care as usual for people with SMD and substance use disorder

Setting: outpatients

Bibliography:

Wilson RP & Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. J Psychopharmacol. 2016; 13(2): 99-111

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	clozapine	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - number of joints per week (follow up: 12 weeks)												
1 ^a	randomised trials	not serious ^b	not serious	not serious	very serious ^c	publication bias strongly suspected ^d	Clozapine, n=15; care as usual (CAU), n=16. Over the 12 weeks, participants in the clozapine group had 4.5 joints less per week on average than the CAU group, though this was not statistically significant (effect size of around 0.6; t=-1.77, d.f. 28.5, p=0.086). ^e				⊕○○○ VERY LOW	CRITICAL
frequency of use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
abstinence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects												
1 ^a	randomised trials	not serious ^b	not serious	not serious	very serious ^f	publication bias strongly suspected ^d	Brunette et (2011) listed 24 different adverse events (taken from Table 3). Of these 3 were statistically different between the two groups: somnolence (clozapine group: n=9/15, 60%; CAU group: n=2/16, 12%); hypersalivation (clozapine: 10/15, 66.7%; CAU: 0/16); constipation (clozapine: n=4/15, 26.7%; CAU: 0/16).				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

- a. Wilson & Batthacharyya (2016) only identified 1 study that assessed this outcome. This open-label study was conducted in the USA, with participants who had been diagnosed with schizophrenia or schizoaffective disorder, and current cannabis use disorder. Clozapine was compared to current usual anti-psychotic medication.
- b. This has been rated as not serious, as study was randomised, outcome assessment was masked, and there was less than 30% drop-out rate. This information was taken from the individual study paper . However, of note, the study was open-label.
- c. This has been rated as very serious, as the number of participants is very low, and the confidence intervals are not provided.
- d. Funnel plots were not produced by the authors of the systematic review (Wilson & Bhattacharyya 2016) Also, one author had shares with a drug manufacturer, and most other authors have received funding and honoraria from drug companies.
- e. This information has been taken from Wilson & Bhattacharyya (2016) (see Table 3) and the individual study.
- f. This has been rated as very serious, as the number of participants was very low, and effect sizes were not provided.

Table 5: Cognitive behaviour therapy (CBT) plus motivational interviewing vs. care as usual for people with SMD and substance use disorder

Author(s): Maya Semrau (first rater), Neerja Chowdhary (second rater)

Date: April 2018

Question: Cognitive behaviour therapy (CBT) plus motivational interviewing compared to care as usual for people with SMD and substance use disorder

Setting: outpatient

Bibliography: Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behaviour therapy (CBT) plus motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - average number of different drugs used during past month (MD below 0 favours intervention) (follow up: 3 months)												
1 ^a	randomised trials	not serious ^b	not serious	serious ^c	very serious ^d	none detected ^e	58	61	-	MD 0.37 higher (0.01 lower to 0.75 higher) ^f	⊕○○○ VERY LOW	CRITICAL
level of consumption - average number of different drugs used during past month (MD below 0 favours intervention) (follow up: 6 months)												
1 ^a	randomised trials	not serious ^b	not serious	serious ^c	very serious ^d	none detected ^e	58	61	-	MD 0.19 higher (0.22 lower to 0.6 higher) ^f	⊕○○○ VERY LOW	CRITICAL
level of consumption - estimated daily consumption of alcohol in past month												
1 ^a	randomised trials	not serious ^b	not serious	serious ^c	very serious ^g	none detected ^e	Level of consumption was higher for the intervention group compared to controls at 3, 6 and 12-month follow-up. However, statistical tests could not be applied due to skewed data. N, intervention group: 21, N, control group: 31 (18 vs 28 at 12-month follow-up). ^h				⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behaviour therapy (CBT) plus motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - estimated daily consumption of amphetamine in past month												
1 ^a	randomised trials	not serious ^b	not serious	serious ^c	very serious ^g	none detected ^e	Data were inconsistent for this outcome at 3, 6 and 12-month follow-up. Data were skewed. N(intervention)=11 (9 at 12-months); N(control)=9 (8 at 12-months). ^h			⊕○○○ VERY LOW	CRITICAL	
frequency of use - cannabis use last 30 days (MD below 0 favours intervention) (at end of treatment) (follow up: 3 months)												
1 ⁱ	randomised trials	very serious ^j	not serious	not serious	very serious ^k	none detected ^e	36	18	-	MD 0.2 lower (2.54 lower to 2.14 higher) ^l	⊕○○○ VERY LOW	CRITICAL
frequency of use - alcohol frequency per month (follow up: 6 months)												
1 ^m	randomised trials	very serious ⁿ	not serious	not serious	very serious ^g	none detected ^e	Frequency of use was higher in the intervention group compared to the control group (mean (intervention)=3.1, SD=3.8; mean(control)=2.3, SD=3.8). N(intervention)=10; N(control)=6. In the same study, alcohol quantity per session was also higher in the intervention group (mean=4.7, SD=2.9, N=10) than in the control group (mean=3.6, SD=2.8, N=6), and mean scores on the AUDIT was also higher in the intervention group (mean=9.3, SD=6.9, N=10) than in the control group (mean=4.8, SD=5, N=6). However, data were skewed for all of these. ^h			⊕○○○ VERY LOW	CRITICAL	
abstinence - proportion of days abstinence from all substances last 90 days												
1 ^o	randomised trials	not serious ^b	not serious	not serious	very serious ^p	none detected ^e	The proportion of days abstinent were higher in the intervention group at 6, 12 and 24 months, but slightly lower at 18 months. Data were skewed. N intervention group at different time points: 129-147; N control group: 117-148. ^h			⊕⊕○○ LOW	CRITICAL	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behaviour therapy (CBT) plus motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
abstinence - average change in % days abstinent during and after treatment												
1 ^o	randomised trials	not serious ^b	not serious	not serious	very serious ^q	none detected ^e	Intervention group: median=19.99 (-25.6 to 83.4), N=17; control group: median=-6.52 (-67.9 to 53.2), N=15. U=86.5, p<0.03. Data summed over 4 time periods (to 12 months) and subtracted from baseline. Data were skewed. ^h				⊕⊕○○ LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - death (RR below 1 favours intervention) (follow up: 1 years)												
3 ^r	randomised trials	not serious ^s	not serious ^t	serious ^u	serious ^v	none detected ^w	6/247 (2.4%)	8/246 (3.3%)	RR 0.72 (0.22 to 2.41) ^x	9 fewer per 1,000 (from 25 fewer to 46 more)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Only 1 study was identified by Hunt et al (2013) for this outcome. The study was conducted in Australia, with people who had either schizophrenia or schizoaffective disorder (75% of sample), and substance abuse disorder (69% alcohol, 74% cannabis, 42% amphetamine). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).

b. This has been rated as not serious, as the study was randomised, there was masking of outcome assessment, and drop-out rates were below 30%. This information was taken from the 'characteristics of included studies' table in Hunt et al 2013.

c. This has been rated as serious, as not all participants had SMD (only 75% of participants).

d. This has been rated as serious, as the number of participants is low, and the confidence interval includes both 'no effect' and appreciable harm.

e. No publication bias was detected, though funnel plots were not produced by the authors of the systematic review (Hunt et al 2013).

f. This information was taken from Analysis 3.5 in Hunt et al (2013).

g. This has been rated as very serious as the number of participants was very low, and data could not be analysed due to skewed data.

h. This information was taken from Analysis 3.7 in Hunt et al (2013).

- i. Hunt et al (2013) only identified 1 relevant study for this outcome. The study was conducted in Ireland, with people with SMD (schizophrenia, other psychosis, MDD and bipolar disorder), and current cannabis dependence. Participants in the intervention group received CBT/MI group sessions for 12 weeks and a booster session at 18 weeks. The CAU group received care from a multi-disciplinary team (cited in Hunt et al (2013)).
- j. This has been rated as very serious, as the drop-out rate was high (42%). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- k. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit and harm.
- l. This information was taken from Analysis 3.6 in Hunt et al 2013.
- m. Only 1 study relevant to this outcome was identified by Hunt et al (2013). The study was conducted in Australia, with people with psychotic disorder, and current alcohol or cannabis use. The intervention (CBT+MI) was received for 4-6 hours. CAU included case management with a focus on substance reduction. This information was taken from the 'characteristics of included studies' in Hunt et al (2013).
- n. This has been rated as very serious, as outcome assessment was not masked. This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- o. Hunt et al (2013) only identified 1 study relevant to this outcome. The study was conducted in the UK, with people with schizophrenia or schizoaffective disorder, and substance abuse disorder. (cited in Hunt et al (2013)).
- p. This has been rated as very serious, as the data could not be analysed due to skewed data.
- q. This has been rated as very serious, as the number of participants was very low, the confidence intervals were very wide, and data were skewed.
- r. Two of the studies were conducted in the UK and 1 in Australia. They all included people with schizophrenia or schizoaffective disorder, and substance use disorder. (see Hunt et al 2013).
- s. This has been rated as not serious, as all studies were randomized, there was masking of outcome assessment, and drop-out rates were below 30% and equal across treatment groups (though drop-out rates varied between 20% and 25% in the 3 studies). This information was taken from the 'characteristics of included studies' tables in Hunt et al 2013.
- t. This was rated as not serious, as heterogeneity was reported to be 8% by Hunt et al 2013 (see Analysis 3.3).
- u. This has been rated as serious, as only 75% of participants had schizophrenia or schizoaffective disorder in 1 of the studies (this information was taken from the 'characteristics of included studies' tables in Hunt et al 2013).
- v. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable harm.
- w. Publication bias was undetected, though funnel plots were not produced by the authors of the systematic review (Hunt et al 2013) due to the low number of studies
- x. This information was taken from Analysis 3.3 in Hunt et al (2013). There was also no significant difference between treatment group for loss to treatment (Analysis 3.1), or death or hospitalisation vs. alive and not admitted to hospital by 24 months (Analysis 3.4) (cited in Hunt et al (2013)).

Table 6: Cognitive behavior treatment vs. care as usual for people with SMD and substance use disorder

Author(s): Maya Semrau (first rater), Neerja Chowdhary (second rater)

Date: April 2018

Question: Cognitive behaviour treatment compared to care as usual for people with SMD and substance use disorder

Setting: outpatient

Bibliography: Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behaviour treatment	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of use - cannabis (CASUAS) ^a												
1 ^b	randomised trials	very serious ^c	not serious	not serious	very serious ^d	none detected ^e	Participants in the intervention group had a slightly higher CASUAS score (mean=1.4, SD=1.4, N=23) than controls (mean=1.3, SD=1.4/1.5, N=24) at both 3 and 6 months. However, data were skewed. ^f			⊕○○○ VERY LOW	CRITICAL	
(non)abstinence - using cannabis in last 4 weeks (RR below 1 favours intervention) (follow up: 3 months)												
1 ^b	randomised trials	very serious ^c	not serious	not serious	very serious ^g	none detected ^e	13/23 (56.5%)	13/24 (54.2%)	RR 1.04 (0.62 to 1.74) ^h	22 more per 1,000 (from 206 fewer to 401 more)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - using cannabis in last 4 weeks (RR below 1 favours intervention) (follow up: 6 months)												
1 ^b	randomised trials	very serious ^c	not serious	not serious	very serious ⁱ	none detected ^e	15/23 (65.2%)	12/24 (50.0%)	RR 1.30 (0.79 to 2.15)	150 more per 1,000 (from 105 fewer to 575 more)	⊕○○○ VERY LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. CASUAS=Cannabis and Substance Use Assessment Schedule. This measures cannabis use and includes information such as percentage of days using cannabis in the past four weeks, frequency of cannabis use, and an index of severity (range 0 to 4) with higher scores indicating greater severity.
- b. Hunt et al (2013) only identified 1 relevant study for this outcome. The study was conducted in Australia with participants who had either schizophrenia, schizoaffective disorder, affective or other psychosis, and were actively using cannabis. The intervention was a cannabis-focused intervention that consisted of a cognitive-behavioural-oriented program delivered in weekly sessions over 3 months. Care as usual consisted of psychoeducation plus standard Early Psychosis Prevention and Intervention Centre (EPPIC) care.
- c. This has been rated as very serious, as drop-out rate was 30%. This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- d. This has been rated as very serious, as the number of participants was very low, and data were skewed.
- e. Publication bias was not detected, though funnel plots were not produced by the authors of the systematic review (Hunt et al 2013).
- f. This information was taken from Analysis 4.4 in Hunt et al (2013).
- g. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes 'no effect'.
- h. This information was taken from Analysis 4.3 in Hunt et al (2013).
- i. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable harm.

Table 7: Motivational interviewing vs. care as usual for people with SMD and substance use disorder

Author(s): Maya Semrau (first rater), Neerja Chowdhary (second rater)

Date: April 2018

Question: Motivational interviewing compared to care as usual for people with SMD and substance use disorder

Setting: inpatients and outpatients

Bibliography: Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - polydrug consumption levels (MD below 0 favours intervention) (follow up: 3 months; assessed with: Opiate Treatment Index (OTI)) ^a												
1 ^b	randomised trials	very serious ^c	not serious	serious ^d	very serious ^e	none detected ^f	43	46	-	MD 0.41 lower (0.91 lower to 0.09 higher) ^g	⊕○○○ VERY LOW	CRITICAL
level of consumption - polydrug consumption levels (MD below 0 favours intervention) (follow up: 12 months; assessed with: Opiate Treatment Index (OTI)) ^a												
1 ^b	randomised trials	very serious ^c	not serious	serious ^d	very serious ^e	none detected ^f	43	46	-	MD 0.07 lower (0.56 lower to 0.42 higher) ^g	⊕○○○ VERY LOW	CRITICAL
level of consumption - change in cannabis use from baseline (MD below 0 favours intervention) (follow up: 3 months)												
1 ^h	randomised trials	not serious ⁱ	not serious	serious ^j	serious ^j	none detected ^f	30	32	-	MD 12.81 lower (23.05 lower to 2.57 lower) ^k	⊕⊕○○ LOW	CRITICAL
level of consumption - change in cannabis use from baseline (MD below 0 favours intervention) (follow up: 6 months)												
1 ^h	randomised trials	not serious ⁱ	not serious	serious ^j	serious ^j	none detected ^f	30	32	-	MD 9.64 lower (18.05 lower to 1.23 lower) ^k	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - change in cannabis use from baseline (MD below 0 favours intervention) (follow up: 12 months)												
1 ^h	randomised trials	not serious ⁱ	not serious	not serious	very serious ^l	none detected [†]	30	32	-	MD 5.82 lower (14.77 lower to 3.13 higher) ^k	⊕⊕○○ LOW	CRITICAL
frequency of use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
(non)abstinence - not abstinent or not improved on all substances (RR below 1 favours intervention) (follow up: 12 months)												
1 ^m	randomised trials	very serious ⁿ	not serious	not serious	very serious ^e	none detected [†]	5/13 (38.5%)	9/12 (75.0%)	RR 0.51 (0.24 to 1.10)	368 fewer per 1,000 (from 75 more to 570 fewer)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - using alcohol (RR below 1 favours intervention) (follow up: 12 months)												
1 ^b	randomised trials	very serious ^c	not serious	serious ^d	very serious ^o	none detected [†]	11/28 (39.3%)	7/24 (29.2%)	RR 1.35 (0.62 to 2.92) ^p	102 more per 1,000 (from 111 fewer to 560 more)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - not abstaining from alcohol (RR below 1 favours intervention) (follow up: 3 months)												
1 ^q	randomised trials	very serious ^r	not serious	not serious	very serious ^e	none detected [†]	6/15 (40.0%)	10/13 (76.9%)	RR 0.52 (0.26 to 1.03) ^s	369 fewer per 1,000 (from 23 more to 569 fewer)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	motivational interviewing	care as usual	Relative (95% CI)	Absolute (95% CI)		
(non)abstinence - not abstaining from alcohol (RR below 1 favours intervention) (follow up: 6 months)												
1 ^q	randomised trials	very serious ^r	not serious	not serious	serious ^t	none detected ^f	5/15 (33.3%)	12/13 (92.3%)	RR 0.36 (0.17 to 0.75) ^s	591 fewer per 1,000 (from 231 fewer to 766 fewer)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - using amphetamine (RR below 1 favours intervention) (follow up: 12 months)												
1 ^b	randomised trials	very serious ^c	not serious	serious ^d	very serious _u	none detected ^f	1/11 (9.1%)	3/8 (37.5%)	RR 0.24 (0.03 to 1.92) ^p	285 fewer per 1,000 (from 345 more to 364 fewer)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - using cannabis (RR below favours intervention) (follow up: 12 months)												
1 ^b	randomised trials	very serious ^c	not serious	serious ^d	very serious _e	none detected [†]	14/28 (50.0%)	22/34 (64.7%)	RR 0.77 (0.49 to 1.21) ^p	149 fewer per 1,000 (from 136 more to 330 fewer)	⊕○○○ VERY LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - death due to all causes (RR below 1 favours intervention) (follow up: 18 months)												
1 ^v	randomised trials	very serious ^w	not serious	not serious	very serious _x	none detected [†]	1/24 (4.2%)	1/25 (4.0%)	RR 1.04 (0.07 to 15.73) ^y	2 more per 1,000 (from 37 fewer to 589 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. This study used the OTI's drug use domain (11 items) to measure drug use over the previous month (28 days) for alcohol, cannabis, amphetamines, cocaine, opiates and other drugs. Clients are asked to estimate the number of drinks or usage of drugs on the two most recent use days in the previous month. Higher scores indicate a greater degree of substance use (cited in Hunt et al (2013), page 19).
- b. Hunt et al (2013) only identified 1 relevant study for this outcome. The study was conducted in Australia, with participants who had schizophrenia (though only 37% of participants) plus substance abuse or dependence (54% alcohol, 51% cannabis, 22% amphetamine, 11% benzodiazepine). The intervention consisted of routine care plus 30-45 minutes of individual motivational interviewing (MI); the control group consisted of routine care plus information that their substance use was at hazardous levels and that they should reduce their substance consumption (cited in Hunt et al (2013)).
- c. This has been rated as very serious, as the drop-out rate was high (44%). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- d. This has been rated as serious, as only a sub-sample of participants had schizophrenia (only 37%). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- e. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit.
- f. No publication bias was detected, though funnel plots were not produced by the authors of the systematic review (Hunt et al 2013).
- g. This information was taken from Analysis 8.7 in Hunt et al (2013).
- h. Hunt et al (2013) only identified 1 study that was relevant to this outcome. The study was conducted in Switzerland, with participants who had schizophrenia, schizoaffective, schizotypal or brief psychotic disorder (92% of participants), plus cannabis misuse (82% of participants met criteria for cannabis dependence). The intervention group received MI for individual plus optional group sessions for up to 6 months. CAU included case management, early intervention and mobile team when needed (cited in Hunt et al (2013)).
- i. This has been rated as not serious, as the study was randomised, there was masking of outcome assessment, and drop-out rates were below 30% (13%). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- j. These have been rated as serious, as the number of participants is very low (imprecision), and only 1 study contributed to the analysis, and therefore the generalisability and applicability of findings is extremely limited (indirectness).
- k. This information was taken from Analysis 8.10 in Hunt et al (2013).
- l. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit and harm.
- m. Hunt et al (2013) only identified 1 study relevant for this outcome. The study was conducted in Australia, with inpatient participants who had a diagnosis of psychotic disorder, plus a diagnosis of substance use disorder (88% alcohol, 76% cannabis, 12% inhalants, 8% cocaine or heroin). The intervention included routine care plus a brief motivational intervention: 3 hours of individual treatment over 6-9 sessions. Care as usual consisted of routine care (pharmacotherapy, access to in-patient programmes and aftercare involving either case management or general practice consultations) (cited in Hunt et al (2013)).
- n. This has been rated as very serious, as the drop-out rate was high (32%). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- o. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable harm.
- p. This information was taken from Analysis 8.6 in Hunt et al (2013).

- q. Hunt et al (2013) only identified 1 study relevant to this outcome. The study was conducted in the USA, with participants who had a diagnosis of schizophrenia and an alcohol use disorder. The intervention consisted of three-session MI. The control group received three-session Educational Treatment (cited in Hunt et al (2013)).
- r. This has been rated as very serious, as there was no masking of outcome assessment (raters were not blinded). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- s. This information was taken from Analysis 8.9 in Hunt et al (2013).
- t. This has been rated as serious, as the number of participants is very low.
- u. This has been rated as very serious, as the number of participants is very low, and the confidence intervals includes both 'no effect' and appreciable benefit and harm.
- v. Hunt et al (2013) only identified 1 relevant study for this outcome. The study was conducted in Australia, with people who had SMD (schizophrenia, MDD, substance-induced psychosis, bipolar disorder) plus substance use (alcohol or cannabis) with psychological dependence. The intervention consisted of 2 brief sessions, which were spaced 2-6 weeks apart. The CAU group received the intervention late, after the 6-month assessment.
- w. This has been rated as very serious, as outcome assessment was not masked, and drop-out rate was 29%. This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- x. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit and harm.
- y. This information was taken from Analysis 8.5 in Hunt et al (2013). There were also no significant differences between treatment groups for loss to treatment at 3 and 6 months (Analysis 8.1) and hospital admission at 12 months (Analysis 8.3) though there was a statistically significant difference in favour of the intervention group for loss to first aftercare appointment (RR 0.69, 0.53 to 0.90, N=48/45). (Analysis 8.4) (cited in Hunt et al (2013)).

Table 8: Contingency management vs. care as usual for people with SMD and substance use disorder

Author(s) Maya Semrau (first rater), Neerja Chowdhary (second rater)

Date: April 2018

Question: Contingency management compared to care as usual for people with SMD and substance abuse disorder

Setting: community

Bibliography: Hunt GE et al. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database of Systematic Reviews. 2013; 10(10): CD001088

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	contingency management	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of use - stimulant use days												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^c	none detected ^d	Stimulant use days were lower for the intervention group than the control group at both 3 months (intervention: mean=0.91, SD=2.4, N=91; control: mean=4.67, SD=7.69, N=85) and 6 months (intervention: mean=1.83, SD=4.94, N=52; control: mean=3.65, SD=7.15, N=55). However, data were skewed. ^e			⊕○○○ VERY LOW	CRITICAL	
frequency of use - days of alcohol												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^c	none detected ^d	Days of alcohol were lower for the intervention group than the control group at both 3 months (intervention: mean=1.84, SD=4.77, N=91; control: mean=4.32, SD=8.43, N=85) and 6 months (intervention: mean=3.6, SD=7.92, N=52; control: mean=4.21, SD=7.86, N=55). However, data were skewed. ^e			⊕○○○ VERY LOW	CRITICAL	
(non)abstinence - stimulant positive urine test (RR below 1 favours intervention) (follow up: 12 weeks)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	serious ^f	none detected ^d	9/91 (9.9%)	28/85 (32.9%)	RR 0.34 (0.17 to 0.68) ^g	217 fewer per 1,000 (from 105 fewer to 273 fewer)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	contingency management	care as usual	Relative (95% CI)	Absolute (95% CI)		
(non)abstinence - stimulant positive urine test (RR below 1 favours intervention) (follow up: 6 months)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	serious ^f	none detected ^d	49/91 (53.8%)	55/85 (64.7%)	RR 0.83 (0.65 to 1.06) ^g	110 fewer per 1,000 (from 39 more to 226 fewer)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - injection use during treatment (RR below 1 favours intervention) (follow up: 3 months)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	serious ^f	none detected ^d	34/91 (37.4%)	56/85 (65.9%)	RR 0.57 (0.42 to 0.77)	283 fewer per 1,000 (from 152 fewer to 382 fewer)	⊕○○○ VERY LOW	CRITICAL
(non)abstinence - injection use during follow-up (RR below 1 favours intervention) (follow up: 6 months)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	very serious ^h	none detected ^d	23/52 (44.2%)	31/55 (56.4%)	RR 0.78 (0.53 to 1.15) ^g	124 fewer per 1,000 (from 85 more to 265 fewer)	⊕○○○ VERY LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - hospitalised (RR below 1 favours intervention) (follow up: 6 months)												
1 ^a	randomised trials	very serious ^b	not serious	not serious	serious ^f	none detected ^d	2/91 (2.2%)	9/85 (10.6%)	RR 0.21 (0.05 to 0.93) ⁱ	84 fewer per 1,000 (from 7 fewer to 101 fewer)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Hunt et al (2013) only identified 1 study relevant to this outcome. The study was conducted in the USA, with participants who had SMD (schizophrenia spectrum, bipolar disorder, MDD), and dependence on stimulants (cocaine, amphetamine, methamphetamine). Intervention: 3 months: negative urine reinforced with selecting prizes or varying value (given a message of “well done” with no financial reward, or with a financial reward of 1 dollar, \$20, or \$80); a positive urine was not reinforced with a chance for a selecting a prize. CAU: were also asked to submit urine for 3 months but they were reinforced positively if their YOKED subject produced a negative urine. These patients provided a urine, but received the reinforcement their “yoked” partner in the active arm received, i.e., they were non-contingently reinforced.
- b. This has been rated as very serious, as drop-out rates were very high (only 42% completed 12 weeks of intervention, and 65% of CAU group). This information was taken from the 'characteristics of included studies' table in Hunt et al (2013).
- c. This has been rated as very serious, as the number of participants was low, and analyses could not be conducted due to skewed data.
- d. Publication bias was not detected, though funnel plots were not produced by the authors of the systematic review (Hunt et al 2013)
- e. This information was taken from Analysis 12.5 in Hunt et al (2013).
- f. This has been rated as serious, as the number of participants is low.
- g. This information was taken from Analysis 12.3 in Hunt et al (2013).
- h. This has been rated as very serious, as the number of participants is low, and the confidence interval includes both 'no effect' and appreciable benefit.
- i. This information was taken from Analysis 12.6 in Hunt et al (2013). There was a significant effect in favour of 'care as usual' for loss to treatment at 3 months (RR 1.65, 1.18 to 2.31, N=176), but there was no significant effect for this at 4 weeks (RR 0.11, 0.01 to 1.90, N=30) (see Hunt et al (2013), Analysis 12.1).

Table 9: Brief intervention (motivational interviewing) compared to education intervention for people with SMD and alcohol misuse

Author(s): First rater: Maya Semrau, second rater: Jayati Das-Munshi

Date: 26 July 2018

Question: Brief intervention (motivational interviewing) compared to education intervention for people with SMD and alcohol misuse

Setting:

Bibliography: Boniface S, Malet-Lambert I, Coleman R, Deluca P, Donoghue K, Drummond C, Khadjesari Z. The Effect of Brief Interventions for Alcohol Among People with Comorbid Mental Health Conditions: A Systematic Review of Randomized Trials and Narrative Synthesis. Alcohol and Alcoholism. 2018; 53(3): 282-293

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	brief intervention (motivational interviewing)	education intervention	Relative (95% CI)	Absolute (95% CI)		
level of consumption												
1	randomised trials	serious ^a	not serious	not serious	very serious _b	none detected ^c	A trial in the USA (N=30) that compared three 1-hour motivational interviewing (MI) sessions with three 1-hour education intervention with CBT components for people with psychosis found no difference in weekly alcohol consumption or peak blood alcohol concentration (BAC) (Graeber et al., 2003). ^d				⊕○○○ VERY LOW	CRITICAL
frequency of use												
1	randomised trials	serious ^a	not serious	not serious	very serious _b	none detected ^c	A trial in the USA (N=30) that compared three 1-hour motivational interviewing (MI) sessions with three 1-hour education intervention with CBT components for people with psychosis found that the MI group had significantly fewer mean drinking days at each time point (4 weeks: MI: 4.60 days vs. ET: 15.15 days; 8 weeks MI: 5.87 days vs. ET: 19.62 days and 24 weeks MI 3.10 days vs. ET: 12.73 days (p<0.01 including baseline measure). (Graeber et al 2003).				⊕○○○ VERY LOW	CRITICAL
abstinence												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	brief intervention (motivational interviewing)	education intervention	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious ^a	not serious	not serious	very serious ^b	none detected ^c	A trial in the USA (N=30) that compared three 1-hour motivational interviewing (MI) sessions with three 1-hour education intervention (ET) with CBT components for people with psychosis and assessed at 4, 8, and 24 weeks found that the MI group had significantly more participants who were abstinent at each time point (4 weeks: MI 66.7% vs. ET 7.7%; MI: 60% vs. ET 23.1%; 24-weeks MI 67.1% vs. ET 7.7% (P < 0.008)) (Graeber et al 2003).				⊕○○○ VERY LOW	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

a. This has been rated as serious, as outcome assessment was not masked in the study. This information was taken from the supplementary material in Boniface et al (2018).

b. This has been rated as very serious, as the total number of participants is very low.

c. Publication bias was not assessed. However, the systematic review (Boniface et al 2018) did search for unpublished studies.

d. This information was taken from Table 2 in Boniface et al (2018).

Table 10: Brief interventions compared to care as usual for people with SMD and alcohol misuse

Author(s): First rater: Maya Semrau, second rater: Jayati Das-Munshi

Date: 26 July 2018

Question: Brief interventions compared to care as usual for people with SMD and alcohol misuse

Setting: inpatients and outpatients

Bibliography: Boniface S, Malet-Lambert I, Coleman R, Deluca P, Donoghue K, Drummond C, Khadjesari Z. The Effect of Brief Interventions for Alcohol Among People with Comorbid Mental Health Conditions: A Systematic Review of Randomized Trials and Narrative Synthesis. *Alcohol and Alcoholism*. 2018; 53(3): 282-293

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	brief interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
level of consumption												
4	randomised trials	serious ^a	very serious ^b	not serious	not serious	none detected ^c	One trial in Sweden (N=344) that entailed immediate personalized telephone feedback from the AUDIT and advice (15 minutes) found a significant difference in AUDIT scores at 6-month follow-up compared to care as usual (P <0.001) (Eberhard et al., 2009). Another trial in Sweden (N=150) that entailed personalized brief advice (15-20 minutes) found that at 12 months, there was an overall reduction in AUDIT scores in the whole sample from 10.9 to 9.8 (F = 10.2, P < 0.01, d = 0.27), but the intervention did not affect AUDIT scores more than care as usual (Nehlin et al 2012). A further trial in Australia (N=160) that entailed motivational interviewing (30-45 minute session) found no significant differences between groups, though overall both groups improved in terms of their alcohol consumption on the OTI (P < 0.01) (Baker et al 2002). Another trial in Australia (N=120) that included 45 minute sessions on the benefits and drawbacks of alcohol use and tailored written feedback also found no significant differences between groups, though the interaction between Time and Group was significant (F = 8.2, df 1,70, P < 0.01) with the motivational group having a higher alcohol consumption at baseline (mean 6.3 (SD 2.5) vs. 5.5 (SD 2.4)) but a lower consumption than the information group at follow-up (mean 2.8 (SD 2.0) vs. 3.6 (SD 1.8)) (Hulse & Tait 2002). ^d				⊕○○○ VERY LOW	CRITICAL
frequency of use												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	brief interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious ^e	not serious	not serious	serious [†]	none detected ^c	One trial in Norway (N=135) that entailed motivational interviewing (2 x 15-minute sessions) found a difference between groups in the frequency of alcohol consumption of 4.7 days per month (95% CI 0.4–9.0) at 24-month follow-up in favour of intervention group compared to care as usual; net difference at 24 months in substance use was 7.3 days per month between intervention and comparison group (95% CI 1.9–12.6, P < 0.01) (Bagoien et al. 2013). ^d				⊕⊕○○ LOW	CRITICAL
abstinence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
relapse rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
frequency of adverse events / side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- This has been rated as serious, as drop-out rates were above 30% in 1 of the studies, and 2 studies had an unclear risk of bias for masking of outcome assessment. This information was taken from the supplementary material in Boniface et al (2018).
- This has been rated as very serious, as the results are inconsistent across the studies, and results could not be pooled due to the large variation between studies.
- Publication bias was not assessed. However, the systematic review (Boniface et al 2018) did search for unpublished studies.
- This information was taken from Table 2 in Boniface et al (2018).
- This has been rated as serious, as drop-out rates were above 30% in the control group. This information was taken from the supplementary material in Boniface et al (2018).
- This has been rated as serious due to the small number of participants.

Table 11: Anti-depressants compared to placebo for people with depression and alcohol dependence

Author(s): First rater: Maya Semrau , second rater: Jayati Das-Munshi

Date: 25th July 2018

Question: Anti-depressants compared to placebo for people with depression and alcohol dependence

Setting: inpatients and outpatients

Bibliography: Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. Cochrane Database of Systematic Reviews. 2018; issue 4, Art. No. CD008581

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-depressants	placebo	Relative (95% CI)	Absolute (95% CI)		
level of consumption - drinks per drinking days (MD below 0 favours antidepressants)												
7 ^a	randomised trials	serious ^b	not serious ^c	serious ^d	not serious	none detected ^e	231	220	-	MD 1.13 lower (1.79 lower to 0.46 lower) ^f	⊕⊕○○ LOW	CRITICAL
level of consumption - drinks per week (MD below 0 favours antidepressants)												
2 ^g	randomised trials	serious ^b	not serious ^h	serious ^d	very serious ⁱ	none detected ^e	28	27	-	MD 5.06 lower (12.3 lower to 2.18 higher) ^j	⊕○○○ VERY LOW	CRITICAL
frequency of use - drinking days per week (MD below 0 favours antidepressants)												
2 ^k	randomised trials	serious ^b	not serious ^l	serious ^d	very serious ⁱ	none detected ^e	28	27	-	MD 1.15 lower (2.35 lower to 0.05 higher) ^m	⊕○○○ VERY LOW	CRITICAL
frequency of use - heavy drinking days per week (MD below 0 favours antidepressants)												
5 ⁿ	randomised trials	serious ^b	serious ^o	serious ^d	serious ^p	none detected ^e	162	151	-	MD 0.33 lower (0.85 lower to 0.2 higher) ^q	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-depressants	placebo	Relative (95% CI)	Absolute (95% CI)		
abstinence - abstinent days (%) (MD above 0 favours antidepressants)												
9 ^r	randomised trials	serious ^b	very serious ^s	serious ^d	serious ^t	none detected ^e	408	413	-	MD 1.34 higher (1.66 lower to 4.34 higher) ^u	⊕○○○ VERY LOW	CRITICAL
abstinence - number of abstinent participants (RR above 1 favours antidepressant)												
7 ^v	randomised trials	serious ^b	not serious ^w	serious ^d	not serious	none detected ^e	70/208 (33.7%)	43/216 (19.9%)	RR 1.71 (1.22 to 2.39) ^x	141 more per 1,000 (from 44 more to 277 more)	⊕⊕○○ LOW	CRITICAL
relapse rates - number of days to first relapse (MD above 0 favours antidepressants)												
6 ^y	randomised trials	serious ^b	serious ^z	serious ^d	serious ^{aa}	none detected ^e	173	175	-	MD 2.54 higher (8.79 lower to 13.87 higher) ^{ab}	⊕○○○ VERY LOW	CRITICAL
frequency of adverse events / side-effects - total adverse events (RR below 1 favours antidepressants)												
5 ^{ac}	randomised trials	serious ^b	serious ^{ad}	serious ^d	not serious	none detected ^e	263/328 (80.2%)	225/316 (71.2%)	RR 1.18 (0.97 to 1.44) ^{ae}	128 more per 1,000 (from 21 fewer to 313 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Six studies were conducted in the USA, and 1 in Australia. Two studies involved nefazodone, 1 sertraline, 1 fluoxetine, 1 imipramine, 1 mirtazapine, and 1 citalopram plus naltrexone (the placebo group also included naltrexone); psychotherapy was included as an additional element in all studies for both the intervention and placebo arms. The studies ranged between 10 and 12 weeks. See Analysis 1.10 and 'Characteristics of included studies' tables in Agabio et al (2018).

b. This has been rated as serious, as none of the studies described whether the outcome assessment was masked. This information has been taken from the 'Characteristics of included studies' tables in Agabio et al (2018).

c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Agabio et al 2018 (see Analysis 1.10).

- d. This has been rated as serious, as the systematic review included people with depression, rather than SMD.
- e. Funnel plots were not produced by the authors of the systematic review (Agabio et al 2018) due to the small number of studies.
- f. This information was taken from Analysis 1.10 in Agabio et al (2018). Note meta-analyses were re-run after removing studies at high risk of bias and continued to indicate that antidepressant versus placebo use was associated with lower drinks per drinking days ((MD: -1.21 drinks/ drinking days (95% CI: -1.91 to -0.51)). The authors of the systematic review (Agabio et al 2018) conducted sub-group analyses for SSRIs and 5-HT2 antagonists, and found significant effects in favour of both groups of drugs; SSRIs: N=271, MD=-1.42, CI:-2.58 to -0.26; 5-HT2 antagonists: N=111, MD=-1.06, CI: -2.0 to -0.11).
- g. Both studies were conducted in the USA. Both studies involved 5-HT2 antagonists: 1 study involved nefazodone, and the other mirtazapine; psychotherapy was included as an additional element in both studies for both the intervention and placebo arms. The studies ranged between 10 and 12 weeks (cited in Agabio et al (2018)).
- h. This was rated as not serious, as heterogeneity was reported to be 0% by Agabio et al (2018) (see Analysis 1.11).
- i. This has been rated as very serious, as the number of participants is very low, and the confidence interval includes both 'no effect' and appreciable benefit and/or harm.
- j. This information was taken from Analysis 1.11 in Agabio et al (2018).
- k. Both studies were conducted in the USA. Both studies involved 5-HT2 antagonists: 1 study involved nefazodone, and the other mirtazapine; psychotherapy was included as an additional element in both studies for both the intervention and placebo arms. The studies ranged between 10 and 12 weeks (cited in Agabio et al (2018)).
- l. This was rated as not serious, as heterogeneity (I²) was reported to be 0% by Agabio et al 2018 (see Analysis 1.9).
- m. This information was taken from Analysis 1.9 in Agabio et al (2018).
- n. Four studies were conducted in the USA, and 1 in Australia. One study involved nefazodone, 1 fluoxetine, 1 imipramine, 1 mirtazapine, and 1 citalopram plus naltrexone (the placebo arm also took naltrexone); psychotherapy was included as an additional element in all studies for both the intervention and placebo arms. The studies ranged between 10 and 12 weeks (cited in Agabio et al (2018)).
- o. This was rated as serious, as heterogeneity (I²) was reported to be 74% by Agabio et al (2018) (see Analysis 1.12)).
- p. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable benefit.
- q. This information was taken from Analysis 1.12 in Agabio et al (2018). The authors of the systematic review (Agabio et al 2018) conducted sub-group analyses for SSRIs and 5-HT2 antagonists, and found no statistically significant effect for either class of drugs; SSRIs: N=189, MD=-0.41, CI: -1.09 to 0.27; 5-HT2 antagonists: N=55, MD=-0.43, CI: -2.09 to 1.22).
- r. Seven of the 9 studies were conducted in the USA, 1 in Australia, and 1 in Spain. Five studies involved sertraline, 1 fluoxetine, 1 nefazodone, 1 imipramine, and 1 citalopram plus naltrexone (the placebo group also received naltrexone); psychotherapy was included as an additional element in all studies for both the intervention and placebo arms. The studies ranged between 10 and 24 weeks (cited in Agabio et al (2018)).
- s. This was rated as very serious, as heterogeneity (I²) was reported to be 80% by Agabio et al (2018)).(see Analysis 1.7).
- t. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable benefit and harm (see Agabio et al (2018), Analysis 1.7).
- u. This information was taken from Analysis 1.7 in Agabio et al (2018). The authors of the systematic review (Agabio et al 2018) conducted sub-group analyses for SSRIs, which similarly found no statistically significant effect (N=711, MD=-0.47 (CI=-3.2 to 2.26)).
- v. All 7 studies were conducted in the USA. Two studies involved sertraline, 2 nefazodone, 1 fluoxetine, 1 imipramine, and 1 sertraline plus naltrexone (vs. naltrexone only); psychotherapy was included as an additional element in all studies for both the intervention and placebo arms. The studies ranged between 10 and 14 weeks (cited in Agabio et al (2018)).
- w. This was rated as not serious, as heterogeneity (I²) was reported to be 0% by Agabio et al (2018) (see Analysis 1.8).
- x. This information was taken from Analysis 1.8 in Agabio et al (2018). Note meta-analyses were re-run after removing studies at high risk of bias and continued to indicate that antidepressant treatment versus placebo were associated with more numbers abstinent (RR: 1.69; 95% CI: 1.18 to 2.43). The authors of the systematic review (Agabio et al 2018) conducted sub-group analyses for SSRIs and 5-HT2 antagonists. The effect was statistically significant in favour of SSRIs (N=250, RR=1.66, CI: 1.02 to 2.68), but not for 5-HT2 antagonists (N=105, RR=1.62, CI: 0.77 to 3.39).
- y. Four studies were conducted in the USA, 1 in Spain, and 1 in Russia. All studies involved SSRIs: 3 studies involved sertraline, 1 sertraline plus naltrexone (vs. naltrexone only), 1 fluoxetine, and 1 escitalopram; psychotherapy was included as an additional element in all studies for both the intervention and placebo arms. The studies ranged between 12 and 24 weeks. (cited in Agabio et al 2018)
- z. This was rated as serious, as heterogeneity (I²) was reported to be 63% by Agabio et al (2018).(see Analysis 1.14).
- aa. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable benefit and harm.
- ab. This information was taken from Analysis 1.14 in Agabio et al (2018).

ac. Three studies were conducted in the USA, 1 in Australia, and 1 in Russia. One study involved sertraline, 1 doxepin, 1 imipramine, 1 escitalopram, and 1 citalopram plus naltrexone (the placebo group also received naltrexone); psychotherapy was included as an additional element in 3 studies for both the intervention and placebo arms. The studies ranged between 3 and 13 weeks. (cited in Agabio et al (2018)).ad. This was rated as serious, as heterogeneity (I^2) was reported to be 71% by Agabio et al (2018) (see Analysis 1.18).

ae. This information was taken from Analysis 1.18 in Agabio et al (2018). The authors of the systematic review (Agabio et al 2018) conducted several sub-group analyses - the only statistically significant effects in favour of placebo were for: total adverse events for TCAs ($N=115$, $RR=1.66$, $CI: 1.13$ to 2.42); insomnia all drugs ($N=564$, $RR=1.69$, $CI: 1.02$ to 2.77); and insomnia SSRIs ($N=469$, $RR=1.75$, $CI: 1.04$ to 2.96). There were no statistically significant effects for: total adverse events for SSRIs; total serious adverse events; withdrawal for medical reasons; dry mouth; headache; dizziness; diarrhoea; nausea; constipation; worsening of clinical condition because of relapse; suicide attempts (see Analysis 1.19 in Agabio et al 2018); and drop-outs (see Analysis 1.17).

Additional evidence not mentioned in GRADE tables³

Interventions for drug-using offenders with co-occurring mental illness

Perry et al (2015) (see also Woodhouse et al 2016) conducted a Cochrane review, to assess the effectiveness of interventions for drug-using offenders with co-occurring mental illness in reducing criminal activity or drug use, or both. Main results: Eight trials with 2058 participants met the inclusion criteria. The methodological quality of the trials was generally difficult to rate due to a lack of clear reporting. Overall, the results could not be combined due to the heterogenous nature of the different study interventions and comparison groups. A narrative summary of the findings identified that the interventions reported limited success with reducing self report drug use, but did have some impact on re-incarceration rates, but not re-arrest. In the single comparisons, moderate-quality evidence was found that therapeutic communities determine a reduction in re-incarceration but reported less success for outcomes of re-arrest, moderate quality of evidence and self report drug use. Three single studies evaluating case management via a mental health drug court (very low quality of evidence), motivational interviewing and cognitive skills (low and very low quality of evidence) and interpersonal psychotherapy (very low quality of evidence) did not report significant reductions in criminal activity and self report drug use respectively. Quality of evidence for these three types of interventions was low to very low. The trials reported some cost information, but it was not sufficient to be able to evaluate the cost-effectiveness of the interventions. Authors' conclusions: Two of the five trials showed some promising results for the use of therapeutic communities and aftercare, but only in relation to reducing subsequent re-incarceration. Overall, the studies showed a high degree of variation, warranting a degree of caution in the interpretation of the magnitude of effect and direction of benefit for treatment outcomes. More evaluations are required to assess the effectiveness of interventions for drug-using offenders with co-occurring mental health problems.

Substance use disorder and SMD

Hunt et al (2013) (see GRADE evidence tables) also looked at integrated models of care vs. care as usual, but found that of the relevant outcomes, there were no statistically significant differences between the two groups for both desirable and undesirable effects.

Bipolar disorder

There have been several further systematic reviews conducted that have assessed interventions for the treatment of substance abuse in people with SMD such as schizophrenia and bipolar disorder. These were not included in the GRADE evidence tables due to their low quality:

1. Salloum & Brown (2017) conducted a narrative review of the public health and clinical significance of substance use disorders (SUDs) in bipolar disorder, including diagnostic and treatment implications, and to evaluate controlled trials conducted to date. Results: 16 treatment studies were identified: 3 psychotherapy, and 13 pharmacotherapy trials. The following medications were evaluated: lithium carbonate, valproate, lamotrigine, topiramate, naltrexone, acamprosate, disulfiram, quetiapine, and citicoline. SUDs have substantial impact on the recognition and management of bipolar disorder. Integrated psychosocial interventions are helpful in decreasing substance abuse. Valproate and naltrexone may decrease alcohol

³ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

use and citicoline may decrease cocaine use and enhance cognition. Authors' conclusions: There is a very limited number of pharmacotherapy and an even smaller number of psychosocial interventions. Our review highlights the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite guidance for clinical practice. *Please note that this paper was given a low AMSTAR rating.*

2. Secades-Alvares & Fernandez-Rodriguez (2017) provided a descriptive overview of different psychological and pharmacological interventions used in the treatment of patients with bipolar disorder and substance abuse, in order to determine their efficacy. A total of 30 experimental studies were grouped according to the type of therapeutic modality described (pharmacological 19; psychological 11). Results: Quetiapine and valproate have demonstrated superiority on psychiatric symptoms and a reduction in alcohol consumption, respectively. Group psychological therapies with education, relapse prevention and family inclusion have also been shown to reduce the symptomatology and prevent alcohol consumption and dropouts. Although there seems to be some recommended interventions, the multicomponent base, the lack of information related to participants during treatment, experimental control or the number of dropouts of these studies suggest that it would be irresponsible to assume that there are well established treatments. *Please note that this paper was given a low AMSTAR rating.*

Schizophrenia

Several other systematic reviews have assessed interventions specifically for the treatment of substance abuse in people with schizophrenia. These were not included in the GRADE evidence tables due to their low quality:

1. Arranz et al (2017) conducted a systematic review on the efficacy of clozapine in SUD improvement in schizophrenic patients. Five studies for nicotine use and nine studies for SUD (other than nicotine) were analyzed. Results: Regarding nicotine use, results from randomized controlled trials (RCT) have found a decrease in nicotine use after 12 weeks of 200-600 mg/day clozapine, as compared with lower doses. In SUD improvement (other than nicotine), RCT have shown superiority of clozapine when compared with risperidone, in short-term studies (from 4 to 12 weeks) performed in cannabis users. In long-term studies (1 year), clozapine was equal to ziprasidone in reducing cannabis use and equal to treatment as usual in reducing alcohol use. The authors concluded that positive results on nicotine use are scarce and derived from studies with a low degree of evidence. Evidence of clozapine on SUD (other than nicotine) is stronger, especially when clozapine is compared with first generation antipsychotics in poly-substance users. When compared with second generation antipsychotics, clozapine was superior to risperidone but equal to olanzapine or ziprasidone in poly-substance and cannabis users. *Please note that this paper was rated as of low quality according to AMSTAR.*
2. De Witte et al (2014) conducted a review on which interventions need to be part of effective outpatient integrated treatment for patients with comorbid schizophrenia and substance use disorders. A total of 14 randomized controlled trials were included. Results: Despite the studies' heterogeneity, the results showed that certain programs (e.g. Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness) and specific interventions (e.g. motivational interviewing, family interventions) seem to be effective. Moreover, programs integrating multiple interventions are more likely to be positively related to better outcomes than single interventions. Finally, the lack of difference between effect sizes of assertive community treatment compared to case management suggests that a lower caseload is not necessary for positive treatment outcomes.

Authors' conclusion: Integrated treatment seems advantageous, although effect sizes are mostly modest. More homogeneous and qualitative sound studies are needed. *Please note that this paper was given a low AMSTAR rating.*

Any mental disorder

Moggi (2016) searched recent meta-analyses and comprehensive reviews on the effectiveness of psychosocial treatments for patients with a comorbidity of psychiatric and substance use disorders (dual diagnosis patients) and were presented as a narrative review for severe (e. g., schizophrenia) and for mild to moderate (e. g., anxiety disorders) dual diagnoses. Results: Promising treatments seem to be integrative stagewise programs that comprise motivational interviewing, cognitive-behavioral interventions, substance use reducing interventions such as relapse prevention and contingency management and/or family interventions. Such programs are mostly superior to control groups (e. g., waiting list) and they are sometimes superior to other active treatments (e. g., treatment as usual) in outcomes of substance use, psychiatric disorders and social functioning. Authors' conclusions: Due to the heterogeneity in patients', treatments', settings', and outcomes' characteristics, it is difficult to generally conclude which psychosocial treatments are effective. Integrated treatments seem to be most effective for dual diagnosis patients.

Antidepressants for the treatment of young people with depression and comorbid substance use disorders

Zhou et al (2014) conducted a systematic review and meta-analysis of the efficacy and tolerability of antidepressants in young people (aged less than 25 years) known to be depressed with comorbid substance use disorder. Their meta-analysis of 5 studies indicated that antidepressants compared to placebo were effective for the treatment of depression in these groups for depression as a dichotomous outcome (RR 1.21 (95% CI: 1.01, 1.45), with weaker evidence to support this observation for depression as a continuous outcome (lower values favour antidepressant) SMD -0.13 (95% CI: -0.55 to 0.30). No differences were found for antidepressant medications versus placebo for substance use outcomes (frequency and quantity of use; SMD 0.10 (95% CI: -0.15 to 0.34) and SMD 0.21 (95% CI: -0.14, 0.55) with lower values favouring medication and no differences for tolerability outcomes (RR 0.99 (95% CI: 0.94 to 1.04)) and suicidal behavior or suicidal ideation (RR 2.21 (95% CI: 0.41 to 11.95)) with lower values favouring medication. *Please note this paper was given a sufficiently high AMSTAR rating to be included but was not, as a more recent, better quality review without age restrictions addressing the same question was used instead (see GRADE Table 11, Agabio et al 2018).*

Alcohol use disorder and SMD

Several systematic reviews have assessed interventions specifically for the treatment of alcohol use disorders in people with SMD. These were not included in the GRADE evidence tables due to their low quality and/or being narrative reviews rather than systematic reviews and/or more relevant systematic reviews being available:

1. Helton & Lohoff (2015) conducted a narrative review on alcohol use disorders (AUDs) and comorbid psychiatric disorders. Currently, there are three medications approved by the U.S. Food and Drug Administration for the treatment of AUDs, and other drugs are being prescribed off-label for this purpose. However, response rates for pharmacologic treatment are low, and extant research suggests that treatment effects may partially depend on genetic factors. Personalized medicine, or using a patient's genetics and/or personal history to determine efficacy of treatment prior to prescription, is an emerging tool that will help clinicians treat their patients more effectively and safely. This review systematically discusses current

findings from AUD pharmacotherapy trials examining disulfiram, acamprosate, naltrexone, the injectable naltrexone, and topiramate. Furthermore, it presents pharmacogenetics findings associated with these medications in an attempt to further the field of personalized medicine. Research from trials examining AUDs and comorbid major depressive disorder and anxiety disorders is also presented, and pharmacogenetic findings for these treatments are discussed. Lastly, the authors comment on the present and future states of the field of personalized medicine for AUD. *Not assessed with AMSTAR, as this is a narrative rather than a systematic review.*

2. Sawicka & Tracy (2017) systematically reviewed the evidence for naltrexone in individuals with both psychosis and alcohol use disorder (AUD). Overall, there is a paucity of research in this important area, with only nine reports meeting search criteria, only four of which were randomized control trials. Studies compared naltrexone with: placebo, another pharmaceutical agent, or upon changes to baseline drinking behaviour. One study evaluated the long-acting injectable formulation of this drug. Results: Most studies, including the methodologically more robust ones, supported naltrexone's effectiveness over placebo in terms of reduction in drinking days and numbers of drinks consumed on such days in this cohort. Work comparing naltrexone to other pharmaceutical interventions showed approximate equivalence with disulfiram, and modest superiority over acamprosate. Authors' conclusions: On this limited evidence base, this review endorses the use of naltrexone as both safe and effective in those with both psychotic illnesses and AUD. Several key issues remain to be elucidated. Critically, study designs meant that they were limited to individuals with good engagement with services, and levels of adherence were attained that are unlikely to be replicated in this cohort in real-world settings. Finally, effects of specific psychosis symptomatology, not least paranoia and insight, upon naltrexone use, and the reverse directional potential of 'double dysphoria' from an opioid antagonist remain largely unexplored. *Please note that this paper was given a low AMSTAR rating.*
3. Riper et al (2014) reviewed published studies on the effectiveness of combining cognitive-behavioural therapy (CBT) and motivational interviewing (MI) to treat comorbid clinical and subclinical alcohol use disorder (AUD) and major depression (MDD) and estimate the effect of this compared with usual care. Twelve studies comprising 1721 patients met the inclusion criteria. The studies had sufficient statistical power to detect small effect sizes. Results: CBT/MI proved effective for treating subclinical and clinical AUD and MDD compared with controls, with small overall effect sizes at post-treatment [$g=0.17$, confidence interval (CI) $=0.07-0.28$, $P<0.001$ for decrease of alcohol consumption and $g=0.27$, CI: $0.13-0.41$, $P<0.001$ for decrease of symptoms of depression, respectively]. Subgroup analyses revealed no significant differences for both AUD and MDD. However, digital interventions showed a higher effect size for depression than face-to-face interventions ($g=0.73$ and $g=0.23$, respectively, $P=0.030$). Authors' conclusions: Combined cognitive-behavioural therapy and motivational interviewing for clinical or subclinical depressive and alcohol use disorders has a small but clinically significant effect in treatment outcomes compared with treatment as usual.

Cannabis use disorder and SMD

McLoughlin et al (2014) conducted a Cochrane review, to assess the effects of specific psychological treatments, anti-psychotics and cannabinoids (cannabis related chemical compounds derived from cannabis or manufactured) for cannabis reduction and/or symptom reduction in people with schizophrenia. Main results: Eight randomised trials, involving 530 participants, were identified which met the selection criteria. For the cannabis reduction studies no one treatment showed superiority for reduction in cannabis use. Overall, data were poorly reported for many outcomes of interest.

1. Reduction in cannabis use: adjunct psychological therapies (specifically about cannabis and psychosis) versus treatment as usual. Results from one

small study showed people receiving adjunct psychological therapies specifically about cannabis and psychosis were no more likely to reduce their intake than those receiving treatment as usual (n = 54, 1 RCT, MD -0.10, 95% CI -2.44 to 2.24, moderate quality evidence). Results for other main outcomes at medium term were also equivocal. No difference in mental state measured on the PANSS positive were observed between groups (n = 62, 1 RCT, MD -0.30 95% CI -2.55 to 1.95, moderate quality evidence). Nor for the outcome of general functioning measured using the World Health Organization Quality of Life BREF (n = 49, 1 RCT, MD 0.90 95% CI -1.15 to 2.95, moderate quality evidence). No data were reported for the other main outcomes of interest 2. Reduction in cannabis use: adjunct psychological therapy (specifically about cannabis and psychosis) versus adjunct non-specific psychoeducation. One study compared specific psychological therapy aimed at cannabis reduction with general psychological therapy. At three-month follow-up, the use of cannabis in the previous four weeks was similar between treatment groups (n = 47, 1 RCT, RR 1.04 95% CI 0.62 to 1.74, moderate quality evidence). Again, at a medium-term follow-up, the average mental state scores from the Brief Psychiatric Rating Scale-Expanded were similar between groups (n = 47, 1 RCT, MD 3.60 95% CI - 5.61 to 12.81, moderate quality evidence). No data were reported for the other main outcomes of interest: global state, general functioning, adverse events, leaving the study early and satisfaction with treatment. 3. Reduction in cannabis use: antipsychotic versus antipsychotic. In a small trial comparing effectiveness of olanzapine versus risperidone for cannabis reduction, there was no difference between groups at medium-term follow-up (n = 16, 1 RCT, RR 1.80 95% CI 0.52 to 6.22, moderate quality evidence). The number of participants leaving the study early at medium term was also similar (n = 28, 1 RCT, RR 0.50 95% CI 0.19 to 1.29, moderate quality evidence). Mental state data were reported, however they were reported within the short term and no difference was observed. No data were reported for global state, general functioning, and satisfaction with treatment. With regards to adverse effects data, no study reported medium-term data. Short-term data were presented but overall, no real differences between treatment groups were observed for adverse effects. 4. Cannabinoid as treatment: cannabidiol versus amisulpride. Again, no data were reported for any of the main outcomes of interest at medium term. There were short-term data reported for mental state using the BPRS and PANSS, no overall differences in mental state were observed between treatment groups. Authors' conclusions: Results are limited and inconclusive due to the small number and size of randomised controlled trials available and quality of data reporting within these trials. More research is needed to a) explore the effects of adjunct psychological therapy that is specifically about cannabis and psychosis as currently there is no evidence for any novel intervention being better than standard treatment for those that use cannabis and have schizophrenia, b) decide the most effective drug treatment in treating those that use cannabis and have schizophrenia, and c) assess the effectiveness of cannabidiol in treating schizophrenia. Currently evidence is insufficient to show cannabidiol has an antipsychotic effect.

Hjorthoj et al (2014) conducted a systematic review that included randomized trials of all types of interventions targeting cannabis use disorders in patients with schizophrenia spectrum disorders. Results: There was no evidence of an effect on frequency of cannabis use, but intervention effects of motivational intervention with or without cognitive behavior therapy were observed on quantity of use and on positive symptoms of schizophrenia. Psychosocial intervention did not have an appreciable effect on negative symptoms. Longer interventions appeared to be more efficacious, and efficacy may be better in trials with comparatively few women. Larger trials may be better at establishing effects on positive symptoms. Authors' conclusion: Psychosocial interventions appear moderately efficacious in reducing quantity of cannabis-use and positive symptoms.

Cocaine dependence and SMD

Sabioni et al (2013) conducted a systematic review, to evaluate and compare the effectiveness of available treatments for cocaine dependence in schizophrenic patients. Studies were identified on typical and atypical antipsychotics and one monoamine transporter antagonist. There were few indications of the effectiveness of atypical antipsychotic medications for the treatment of cocaine dependence in patients with schizophrenia. Authors' conclusions: We suggest that further studies be conducted with atypical antipsychotic medications and greater methodological strictness, including

using a placebo group in the studies, so that health professionals can determine the real effectiveness of this class of medication for the treatment of cocaine dependence in schizophrenic patients. *Please note that this paper was given a low AMSTAR rating.*

Methamphetamine use disorders and depression

Hellem et al (2015) conducted a systematic review on treatment strategies for co-occurring depression and methamphetamine use disorders. Research articles describing psychological (n = 3), pharmacological (n = 6), nutritional supplement (n = 1), and psychological combined with pharmacological (n = 3) approaches for the treatment of methamphetamine use or withdrawal and/or depression were included. Results and conclusions: Psychological and combination of psychological with pharmacological approaches have not been shown to be effective in treating these co-occurring conditions. Antidepressants have been determined to be ineffective and/or to introduce side effects. Gender differences with response to treatment were examined in only one of the published studies. There is a large gap in knowledge regarding treatment of co-occurring methamphetamine use disorders and depression. Considering that female methamphetamine users experience higher rates of depression than men, a focus on gender-specific treatment approaches is warranted.

Relevant guidelines

NICE guidelines *Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings* (Clinical guideline [CG120]; Published date: March 2011):

- Identify and provide support to people with coexisting severe mental illness and substance misuse; consider multiple needs.
- Ensure the safeguarding needs of all people with coexisting severe mental illness and substance misuse, and their carers and wider family, are met.
- Ensure the person is referred to and followed up within secondary care, and that mental health services take the lead for assessment and care planning.
- Involving people with coexisting severe mental illness and substance misuse in care planning

NICE guidelines *Psychosis and schizophrenia in adults: prevention and management* (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014) and NICE guidelines *Bipolar disorder: assessment and management* (Clinical guideline [CG185]; Published date: September 2014 Last updated: February 2016):

- Treatment in line with NICE guidance for substance misuse, if detected as a part of assessment and care planning (in secondary care)
- Re antipsychotic medication: discuss use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs, and possible interference with therapeutic effects of prescribed medication/psychological treatments.
- For a person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is: comorbid substance misuse.

NICE guidelines *Depression in adults with a chronic physical health problem: recognition and management* (Clinical guideline [CG91]; Published date: October 2009):

- If complex/severe depression and comorbid alcohol or substance misuse, referral to specialist MH services.
- Recommendations to avoid excess eating, smoking, or alcohol, re: advice on sleep hygiene.

Cooper et al (2016)'s BAP guidelines included the following recommendations about comorbid alcohol misuse and psychosis:

- The negative impact of harmful alcohol use, abuse or dependence in people with schizophrenia requires that their alcohol use, as well as use of other substances, is assessed and that treatment is appropriately focused on any harmful substance use, abuse or dependence.
- Optimisation of antipsychotic treatment, following existing guidance, may have a role to play in reducing substance misuse.
- Clozapine should be considered in patients with persisting harmful substance use, abuse or dependence, because it has been reported to reduce substance use and improve psychosis, but the supporting data are still preliminary.
- Specific medication for relapse prevention in patients with alcohol dependence should be considered, such as naltrexone or acamprosate.

Crockford & Addington (2017)'s Canadian Schizophrenia Guidelines: Schizophrenia and Other Psychotic Disorders with Coexisting Substance Use Disorders:

The authors conducted a review to identify evidence-based practices best practices that improve outcomes for individuals with schizophrenia and substance used disorders. Guidelines were reviewed that were published in the last 5 years and that included systematic reviews or meta-analyses. Most of their recommendations came from 2 publications from the National Institute for Health and Care Excellence (NICE): the 2011 guidance titled *Coexisting Severe Mental Illness (Psychosis) and Substance Misuse: Assessment and Management in Healthcare Settings* and the 2014 guidance titled *Psychosis and Schizophrenia in Adults: Prevention and Management*. These recommendations were placed into the Canadian context to create this guideline. Results: Evidence supports the inclusion of individuals with coexisting substance use disorders in first-episode psychosis programs. The programs should integrate psychosis and substance use treatments, emphasizing ongoing monitoring of both substance use and patterns and symptoms. The best outcomes are achieved with combined use of antipsychotic medications and addiction-based psychosocial interventions. However, limited evidence is available to recommend using one antipsychotic medication over another or one psychosocial intervention over another for persons with schizophrenia and other psychotic disorders with coexisting substance use disorders. Authors' conclusions: Treating persons who have schizophrenia and other psychotic disorders with coexisting substance use disorders can present clinical challenges, but modifications in practice can help engage and retain people in treatment, where significant improvements over time can be expected.

Hasan et al (2015)'s World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia made the following recommendations:

—Clozapine seems to be effective for the reduction of craving and substance intake in patients with a dual diagnosis of schizophrenia and alcohol use disorder and other substance use disorder. It has to be considered that due to the high non-compliance in this patient group the long titration period when initiating treatment again may limit the use of clozapine. Special caution is required as patients with alcohol use disorders are at-risk to develop diseases of the blood-forming system (e.g., macrocytic anaemia, but also pancytopenia) or depression of

- bone marrow that may increase the risk for clozapine-induced agranulocytosis. Furthermore, comorbid alcohol use disorder may potentiate clozapine-induced cardiac toxicity.
- Some antipsychotics seem to be effective in patients with a dual diagnosis of schizophrenia and alcohol use disorder for the reduction of craving and substance intake.
 - Other antipsychotics (FGA and SGA) show limited positive evidence in schizophrenia patients with cocaine use disorder for the reduction of craving and substance intake as detailed above.
 - An inconsistent superiority of SGAs compared to FGAs in the reduction of craving and the amount of the used substance can be assumed.
 - Due to the high non-compliance in dual diagnosis patients the preferred use of long-acting injectables is useful.

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Methadone has significant interactions with multiple psychiatric medications. Sedating effects: It is recommended to avoid concurrent use with sedating agents (such as **amitriptyline**, **haloperidol**, **risperidone**, **chlorpromazine**, **fluphenazine**, **clozapine**, and **diazepam**) if possible, as concurrent use may increase the risk of CNS depression*. If using methadone with one of these medications, use the lowest doses possible and for the shortest amount of time possible. Monitor for clinical signs of CNS depression including sedation, confusion, low blood pressure and decreased respiration. QT-interval prolongation: Avoid using methadone with **fluoxetine**, as the latter is considered to confer high risk with regards to QT interval prolongation, and methadone may increase this effect. Additionally, **methadone**, **haloperidol**, **risperidone**, **chlorpromazine**, and **clozapine** all confer moderate risk of QT-interval prolongation. If using methadone with one of these medications, monitor for sedation as above and monitor for QT-prolongation and arrhythmias on ECG. Lithium carries indeterminate risk for QT-prolongation and may be a risk-modifier; monitor for QT-prolongation and arrhythmias on ECG if possible. Serotonergic effects: Methadone can have serotonergic effects; if used with **amitriptyline** or **lithium**, monitor

clinically for signs of serotonin syndrome including confusion, neuromuscular excitability and dysautonomia. Other effects: Monitor concurrent therapy with anticholinergic medications such as **biperiden** or **trihexyphenidyl**, as they may increase the risk of side effects and toxicity of methadone including urinary retention and constipation. Levels and efficacy of **methadone** may be reduced by carbamazepine, as the latter is a strong CYP3A4 inducer.

Buprenorphine has significant interactions with multiple psychiatric medications. Sedating effects: Concurrent use of sedating agents (such as **haloperidol**, **risperidone**, **chlorpromazine**, **fluphenazine**, **clozapine**, **carbamazepine**, and **diazepam**) with buprenorphine may increase the risk of CNS depression*. Avoid concurrent use if there are concerns for risk of buprenorphine misuse (either using too much or injecting). Concurrent use on an outpatient basis may not be appropriate in persons who are taking high doses of other CNS depressants or if there is significant use of alcohol. If used together, consider decreasing the other sedating agent and starting buprenorphine at a low dose. Monitor for clinical signs of CNS depression including sedation, confusion, low blood pressure and decreased respiration. Serotonergic effects: Opioid medications such as buprenorphine can increase the risk of serotonin toxicity or serotonin syndrome if used with **amitriptyline** or **fluoxetine** or **lithium**. Monitor clinically for signs of serotonin syndrome including confusion, neuromuscular excitability, and dysautonomia. QT-interval prolongation: Monitor therapy with **fluoxetine**, as fluoxetine is considered to confer high-risk for QT interval prolongation and buprenorphine may increase this risk, though the evidence is unclear. Monitor ECG if possible. Other effects: Monitor concurrent therapy with anticholinergic medications such as **biperiden** or **trihexyphenidyl**, as they may increase the risk of side effects and toxicity of buprenorphine including urinary retention and constipation.

*Of note, the US Food & Drug Administration (FDA) issued a safety announcement in 2017⁴ regarding the use of methadone and buprenorphine with other sedating medications. While the risks of CNS sedation can be serious, they may be outweighed by the risk of other harms of untreated opioid use disorders. Thus, the US FDA does not recommend withholding opioid replacement therapy in the context of other sedating medications; cautious medication management is advised.

See Annex for further details.

⁴ United States Food and Drug Administration. Drug Safety and Availability - FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. <https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm>

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of findings table

	Outcome	Relative risk (RR) <i>value above 1 favours intervention unless specified otherwise</i>	Mean difference (MD) <i>positive value favours intervention unless specified otherwise</i>
GRADE Table 1 (Temmingh et al 2018) Risperidone vs. olanzapine	level of consumption	N/A	MD 0.4 higher (4.72 lower to 5.52 higher) VERY LOW
	frequency of use	N/A	
	abstinence – stopping cannabis use	RR 1.19 (0.68 to 2.08) LOW	N/A
	abstinence – stopping alcohol use	RR 1.31 (0.73 to 2.36) LOW	N/A
	relapse rates	N/A	
	frequency of adverse events / side-effects – Parkinsonism	N/A	MD 0.08 lower (1.21 lower to 1.05 higher) VERY LOW <i>negative values favour intervention</i>
GRADE Table 2 (Temmingh et al 2018) Risperidone vs. clozapine	level of consumption	N/A	
	frequency of use	RR 1.00 (0.30 to 3.35) VERY LOW	N/A

	abstinence	RR 1.13 (0.41 to 3.12) VERY LOW	N/A
	relapse rates	N/A	
	frequency of adverse events / side-effects – any extrapyramidal	RR 2.71 (0.30 to 24.08) VERY LOW <i>value below 1 favours intervention</i>	N/A
GRADE Table 3 (Wilson & Bhattacharyya 2016) Ziprasidone vs. clozapine	level of consumption	Narrative review. Level of consumption significantly reduced in both groups, with no significant difference between groups. VERY LOW	
	frequency of use	N/A	
	abstinence	N/A	
	relapse rates	N/A	
	frequency of adverse events / side-effects	Narrative review. Significantly more side-effects in clozapine group. VERY LOW.	
GRADE Table 4 (Wilson & Bhattacharyya 2016) Clozapine vs. care as usual	level of consumption	Narrative review. No statistically significant difference between groups. VERY LOW	
	frequency of use	N/A	
	abstinence	N/A	
	relapse rates	N/A	
	frequency of adverse events / side-effects	Narrative review. 3 out of 24 adverse events significantly more common in clozapine group compared to CAU. VERY LOW	

GRADE Table 5 (Hunt et al 2013) Cognitive behaviour therapy (CBT) plus motivational interviewing vs. care as usual	level of consumption- average number of different drugs used during past month (3 months)	N/A	MD 0.37 higher (0.01 lower to 0.75 higher) VERY LOW <i>negative values favour intervention</i>
	level of consumption – average number of different drugs used during past month (6 months)	N/A	MD 0.19 higher (0.22 lower to 0.6 higher) VERY LOW <i>negative values favour intervention</i>
	level of consumption – estimated daily consumption of alcohol in past month	Narrative review. Data skewed but not in favour of intervention. VERY LOW	
	level of consumption – estimated daily consumption of amphetamine in past month	Narrative review. Data skewed; inconsistent results. VERY LOW	
	frequency of use – cannabis use last 30 days	N/A	MD 0.2 lower (2.54 lower to 2.14 higher) VERY LOW <i>negative values favour intervention</i>
	frequency of use – alcohol frequency per month	Narrative review. Data skewed but not in favour of intervention. VERY LOW	
	abstinence – proportion of days abstinence from all substances last 90 days	Narrative review. Data skewed, but generally in favour of intervention (though not consistently). LOW	
	abstinence – average change in % days abstinent during and after treatment	Narrative review. Data skewed but in favour of intervention. LOW	
	relapse rates	N/A	
	frequency of adverse events / side-effects –	RR 0.72	N/A

	death	(0.22 to 2.41) LOW <i>value below 1 favours intervention</i>	
GRADE Table 6 (Hunt et al 2013) Cognitive behavior treatment vs. care as usual	level of consumption	N/A	
	frequency of use – cannabis	Narrative review. Skewed data but not in favour of intervention. VERY LOW	
	(non)abstinence – using cannabis in last four weeks (3 months)	RR 1.04 (0.62 to 1.74) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence – using cannabis in last four weeks (6 months)	RR 1.30 (0.79 to 2.15) VERY LOW <i>value below 1 favours intervention</i>	N/A
	relapse rates	N/A	
	frequency of adverse events / side-effects	N/A	
GRADE Table 7 (Hunt et al 2013) Motivational interviewing vs. care as usual	level of consumption – polydrug consumption levels (3 months)	N/A	MD 0.41 lower (0.91 lower to 0.09 higher) VERY LOW <i>negative values favour intervention</i>
	level of consumption – polydrug consumption levels (12 months)	N/A	MD 0.07 lower (0.56 lower to 0.42 higher) VERY LOW <i>negative values favour intervention</i>
	level of consumption –	N/A	MD 12.81 lower

	change in cannabis use from baseline (3 months)		(23.05 lower to 2.57 lower) LOW <i>negative values favour intervention</i>
	level of consumption – change in cannabis use from baseline (6 months)	N/A	MD 9.64 lower (18.05 lower to 1.23 lower) LOW <i>negative values favour intervention</i>
	level of consumption – change in cannabis use from baseline (12 months)	N/A	MD 5.82 lower (14.77 lower to 3.13 higher) LOW <i>negative values favour intervention</i>
	frequency of use	N/A	
	(non)abstinence - not abstinent or not improved on all substances	RR 0.51 (0.24 to 1.10) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence - using alcohol	RR 1.35 (0.62 to 2.92) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence - not abstaining from alcohol (3 months)	RR 0.52 (0.26 to 1.03) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence -	RR 0.36	N/A

	not abstaining from alcohol (6 months)	(0.17 to 0.75) VERY LOW <i>value below 1 favours intervention</i>	
	(non)abstinence - using amphetamine	RR 0.24 (0.03 to 1.92) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence - using cannabis	RR 0.77 (0.49 to 1.21) VERY LOW <i>value below 1 favours intervention</i>	N/A
	relapse rates	N/A	
	frequency of adverse events / side-effects – death due to all causes	RR 1.04 (0.07 to 15.73) VERY LOW <i>value below 1 favours intervention</i>	N/A
GRADE Table 8 (Hunt et al 2013) Contingency management vs. care as usual	level of consumption	N/A	
	frequency of use – stimulant use days	Narrative review. Skewed data but in favour of intervention. VERY LOW	
	frequency of use – days of alcohol	Narrative review. Skewed data but in favour of intervention. VERY LOW	
	(non)abstinence – stimulant positive urine test (12 weeks)	RR 0.34 (0.17 to 0.68) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence –	RR 0.83	N/A

	stimulant positive urine test (6 months)	(0.65 to 1.06) VERY LOW <i>value below 1 favours intervention</i>	
	(non)abstinence – injection use during treatment (3 months)	RR 0.57 (0.42 to 0.77) VERY LOW <i>value below 1 favours intervention</i>	N/A
	(non)abstinence – injection use during follow-up (6 months)	RR 0.78 (0.53 to 1.15) VERY LOW <i>value below 1 favours intervention</i>	N/A
	relapse rates	N/A	
	frequency of adverse events / side-effects – hospitalised	RR 0.21 (0.05 to 0.93) VERY LOW <i>value below 1 favours intervention</i>	N/A
Grade Table 9 (Boniface et al 2018) Brief motivational interviewing vs educational treatment (ET) (control group) for SMD and alcohol use disorders	Level of consumption	Narrative review- one study Not in favour of intervention VERY LOW	
	Frequency of use	Narrative review- one study Intervention group had fewer drinking days at 24 weeks' follow up (3.10 drinking days in MI group vs. 12.73 drinking days in ET group) VERY LOW	
	Abstinence	Narrative review- one study More participants abstinent in the intervention group at 24 weeks' follow up (67.1% in MI group vs. 7.7% in ET group) VERY LOW	

Grade table 10 (Boniface et al 2018) Brief interventions[†] vs. care as usual in people with SMD and alcohol/substance use disorders	Level of consumption	Narrative review: Various brief interventions with varying length of follow up and types of intervention [†] - mixed findings VERY LOW (estimate from one study)	
	Frequency of use (days per month) at 24 month follow-up	MD:7.26 lower (12.64 lower to 1.89 lower) (MD below 0 favours intervention) LOW	
Grade table 11 (Agabio et al 2018) Antidepressants compared to placebo for people with depression and comorbid alcohol dependence	Level of consumption- drinks per drinking days	N/A	MD 1.13 lower (1.79 lower to 0.46 lower) (MD below 0 favours antidepressants) LOW
	Level of consumption- drinks per week	N/A	MD 5.06 lower (12.3 lower to 2.18 higher) (MD below 0 favours antidepressants) VERY LOW
	Frequency of use- drinking days per week	N/A	MD 1.15 lower (2.35 lower to 0.05 higher) (MD below 0 favours antidepressants) VERY LOW
	frequency of use - heavy drinking days per week	N/A	MD 0.33 lower (0.85 lower to 0.2 higher) (MD below 0 favours antidepressants) VERY LOW
	abstinence - abstinent days (%)	N/A	MD 1.34 higher (1.66 lower to 4.34 higher) (MD above 0 favours antidepressants)

			VERY LOW
	abstinence - number of abstinent participants	RR 1.71 (1.22 to 2.39) (RR above 1 favours antidepressant) LOW	N/A
	relapse rates- number of days to first relapse	N/A	MD 2.54 higher (8.79 lower to 13.87 higher) (MD above 0 favours antidepressants) VERY LOW
	frequency of adverse events / side-effects - total adverse events	RR 1.18 (0.97 to 1.44) (RR below 1 favours antidepressants) VERY LOW	N/A

[†] Range of brief interventions included: immediate personalised telephone feedback, personalised brief advice, motivational interviewing, brief session on benefits/ drawback of alcohol use and tailored written feedback

Evidence to Decision Table

	JUDGEMENT	EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes - X Yes ○ Varies ○ Don't know	• There is high co-morbidity between SMD and substance use disorder; substance abuse is the most prevalent comorbid psychiatric condition associated with schizophrenia. • People with a SMD are at a higher risk of developing a substance use disorder, and vice versa. • Comorbid mental disorders amongst people with substance use disorder may also be an important risk factor for severe substance-use related outcomes, such as (non-fatal) overdoses and suicide, and continued substance (e.g. cannabis) use after onset of psychosis may be linked to higher relapse rates, longer hospital admissions, and more severe positive symptoms. • There may also be a dose-response relationship between level of substance use and risk of mental disorder.	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ○ Trivial - X Small ○ Moderate ○ Large ○ Varies ○ Don't know	The desirable anticipated effects vary for the different interventions included in this review: • Risperidone vs. olanzapine: There were small effects in favour of risperidone for level of consumption and abstinence (both alcohol and drugs), though these were not statistically significant. There were no data available for frequency of use and relapse rates. • Risperidone vs. clozapine: A very small effect was found in favour of risperidone compared to clozapine for abstinence, though this was not statistically significant. There was no difference between the two drugs in terms of frequency of substance use. There were no data available for level of consumption and relapse rates. • Ziprasidone vs. clozapine: Level of consumption was	Many of the trials were under-powered with null effects; there was equivocal direct evidence for desirable anticipated effects. There is good indirect evidence that certain interventions work for alcohol and substance use disorders in non-SMD populations- see the MHGAP guidelines

		significantly reduced in both groups, but there was no significant difference between groups. There were no data available for the other outcomes. • Clozapine vs. care as usual: There was no statistical difference between the two groups in terms of level of consumption. There were no data available for the other outcomes. • CBT plus motivational interviewing vs. care as usual: For level of consumption, the effect size was either in favour of care as usual, though not statistically significant, or data were skewed and inconsistent. For frequency of use, data were inconsistent, with some of the data skewed. For abstinence, data were generally in favour of the interventions, though not consistently and data were skewed. There were no data available for relapse rates. • Cognitive behaviour treatment vs. care as usual: Data for frequency of use were skewed and in favour of care as usual. There was a small effect in favour of care as usual for (non)abstinence, though this was not statistically significant. There were no data available for level of consumption and relapse rates. • Motivational interviewing vs. care as usual: There was a small effect in favour of the intervention for (polydrug) level of consumption at two time points (though this was not statistically significant), and a substantial effect in favour of the intervention for level of consumption (change in cannabis use from baseline), which was statistically significant in the short and medium term, but not in the long-term. In regards to (non)abstinence, there was a substantial and significant effect in favour of the intervention for non-abstinence from alcohol at 6 months, a small to moderate but statistically non-significant effect in favour of the intervention for non-abstinence from alcohol at 3 months, non-abstinence or no improvement on all substances, using amphetamine and using cannabis, and a	
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	small but statistically non-significant effect in favour of care as usual for using alcohol. There were no data available for frequency of use and relapse rates. • Contingency management vs. care as usual: There were only skewed data available for frequency of use, though these were in favour of the intervention. For (non)abstinence, there was a substantial and statistically significant effect in favour of the intervention for stimulant positive urine test in the short-term and for injection use during treatment at 3 months; there was a moderate but statistically non-significant effect for both stimulant positive urine test and injection use during treatment at 6 months. There were no data available for level of consumption and relapse rates. • Brief motivational interviewing intervention versus an educational intervention control for alcohol use disorders comorbid with SMD: (All estimates from one small pilot study)-motivational interviewing was associated with greater abstinence and lower drinking days compared to the educational control at 24 weeks' follow up. • Brief interventions vs. a minimally active comparator for people with SMD and comorbid substance/ alcohol use; a. immediate personalised feedback- associate with improved AUDIT scores at 6 month follow up compared to control; b. 15-20 minutes of personalised brief advice did not impact on AUDIT scores in intervention vs. control group at 12-month follow-up; c. 30-45 minutes motivational interviewing session did not improve levels of consumption in intervention vs. control group; d. 45 minute intervention detailing benefits/ drawback of alcohol use with tailored written feedback was associated with higher alcohol consumption in the intervention group at baseline with lower consumption at follow-up compared to the control group. • Brief motivation intervention (2 sessions) compared to care-as-usual was associated with a reduction in frequency of use	
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		(substance/ alcohol) misuse at 24 month follow-up. Antidepressants vs placebo for depression comorbid with alcohol dependence. Antidepressants compared to placebo in people with depression and AUD were associated with a lower number of drinks per drinking days (Mean difference -1.13 (95% CI: -1.79 to -0.49) and with a small effect favouring antidepressant with respect to numbers abstinent, compared to placebo (RR 1.71 (95% CI: 1.22 to 2.39). Although levels of consumption (drinks per week), frequency of use (drinking days per week), frequency of heavy drinking days per week, were lower and number of abstinent days as well as days to first relapse were higher in the antidepressant group compared to placebo, 95% confidence intervals spanned the null for each of these outcomes.	
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? - Large - Moderate - Small - Trivial X Varies - Don't know	The undesirable anticipated effects vary for the different interventions included in this review: - Risperidone vs. olanzapine: There was a very small effect in favour of risperidone for frequency of adverse events / side-effects (Parkinsonism), but this was not statistically significant. There was also no significant difference between groups in weight gain. - Risperidone vs. clozapine: There was a substantial effect in favour of clozapine in regards to frequency of adverse events / side-effects (any extrapyramidal), though this was not statistically significant. There were no significant differences for the 20 other adverse events assessed either. - Ziprasidone vs. clozapine: Significantly more side-effects in clozapine group, in particular in regards to hypersalivation. - Clozapine vs. care as usual: 3 out of 24 adverse events	Undesirable anticipated effects for pharmacological interventions were moderate. Undesirable anticipated effects for non-pharmacological effects were trivial.

	significantly more common in the clozapine group compared to CAU (omnolence; hypersalivation; constipation). • CBT plus motivational interviewing vs. care as usual: Small effect in favour of intervention for death rates, though this was not statistically significant. There was also no significant difference for loss to treatment, or death or hospitalisation vs. alive and not admitted to hospital. • Cognitive behaviour treatment vs. care as usual: No data available. • Motivational interviewing vs. care as usual: Very small effect in favour of care as usual, which was not statistically significant. There were also no significant differences for loss to treatment and hospital admission, though there was a statistically significant difference in favour of the intervention group for loss to first aftercare appointment. • Contingency management vs. care as usual: Substantial effect in favour of intervention for frequency of adverse events / side-effects (hospitalisation), which was statistically significant. There was a significant effect in favour of 'care as usual' for loss to treatment at 3 months, but there was no significant effect for this at 4 weeks. • For antidepressants compared to placebo for people with depression and AUD: Total adverse events in antidepressants compared to placebo were more frequent although overall did not reach statistical significance. In sub-group analyses more adverse effects were noted for TCAs (RR 1.66 (95% CI: 1.13 to 2.42) and insomnia (all antidepressants RR 1.69 (95% CI: 1.02 to 2.77; SSRIs: RR: 1.75 (95% CI: 1.04 to 2.96)	
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CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of effects was VERY LOW for all interventions and outcomes, apart from for the following associations, which had a LOW certainty of the evidence of effects: • Risperidone vs. olanzapine: abstinence (cannabis and alcohol) • CBT plus motivational interviewing vs. care as usual: abstinence (proportion of days abstinence from all substances last 90 days, average change in % days abstinent during and after treatment), frequency of adverse events / side-effects (death) • Motivational interviewing vs. care as usual: level of consumption (change in cannabis use from baseline at 3, 6 and 12 months) • Antidepressants versus placebo for people with depression and comorbid alcohol dependence: Level of consumption (drinks per drinking day) were lower with antidepressant use vs. placebo • Antidepressants versus placebo for people with depression and comorbid alcohol dependence: There were a larger number of abstinent participants in the antidepressant group compared with the placebo group	There is indirect evidence for evidence of effects in MHGAP guidelines- this was noted to be of LOW quality.
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? X Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012)	Preferences may vary between different stakeholder groups

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison - X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	• CBT plus motivational interviewing vs. care as usual: Of the outcomes assessed, there were no statistically significant differences (or data were skewed and could not be statistically assessed) between the two groups for both desirable and undesirable effects. • Cognitive behaviour treatment vs. care as usual: Of the outcomes assessed, there were no statistically significant differences (or data were skewed and could not be statistically assessed) between the two groups for desirable effects, and there were no data available for undesirable effects. • Motivational interviewing vs. care as usual: There is a balance in favour of the intervention, as the intervention had significant benefits for level of consumption (change in cannabis use from baseline) (though possibly not in the long-term), and for (non)abstinence from alcohol at 6 months (though not at 3 months). There was also a statistically significant difference in favour of the intervention group for loss to first aftercare appointment. • Contingency management vs. care as usual: There is a slight balance in favour of the intervention, as there was a substantial and statistically significant effect in favour of the intervention for (non)abstinence (stimulant positive urine test, and injection use during treatment at 3 months), and there was also a substantial and statistically significant effect in favour of the intervention for frequency of adverse events / side-effects (hospitalisation). However, there was a significant effect in favour of 'care as usual' for loss to treatment at 3 months, though this was not significant at 4 weeks.	There is insufficient direct evidence to favour the intervention There is indirect evidence in support of interventions for SUD and AUD- refer to MHGAP guidelines
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RESOURCES REQUIRED	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies - X Don't know	The resource requirements for the pharmacological interventions is likely to be lower than for the non-pharmacological interventions (due to the elevated training and human resource costs associated with non-pharmacological interventions). For CBT plus motivational interviewing, the direct cost has been estimated to be: mean=US\$329 (SD=649), N=61; CAU mean: US\$180 (SD=201), N=49 (Bellack 2006, in Hunt et al 2013).	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High - X No included studies	No direct evidence identified on this.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies - X No included studies	No direct evidence identified for this.	

EQUITY	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact - X Probably increased ○ Increased ○ Varies ○ Don't know	No direct evidence identified for this.	There is a need for effective implementation There is a lack of direct evidence
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes - X Varies ○ Don't know	No direct evidence identified for this.	
FEASIBILITY	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes - X Varies ○ Don't know	All studies were conducted in high-income countries in Europe and North America, such as the USA, Netherlands, Australia, UK, Germany and Ireland. None of the included studies were conducted in LMICs. Of the reviewed pharmacological interventions, only risperidone and clozapine are included in the essential medicines list. For the non-pharmacological interventions, although intervention features, such as duration or frequency, could possibly be adapted for each particular setting, e.g. by being administered by suitably trained and supported non-specialists, there is no direct evidence available to support this.	The following will need to be taken into consideration: workforce, type of intervention, country, service users' preferences.

WHO guidelines for general population

The mhGAP Intervention guide recommends the following:

- Alcohol dependence:
 - Thiamine during alcohol use
 - Diazepam during alcohol detoxification to treat withdrawal symptoms
 - Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification
 - Psychosocial interventions if available, e.g. cognitive behaviour therapy (CBT), motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups
- Drug dependence:
 - For opioid withdrawal: buprenorphine, methadone, clonidine, lofexidine
 - Psychosocial interventions if available, e.g. CBT, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups

GDG Recommendations

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

TYPE OF RECOMMENDATION	Strong recommendation against the option ○	Conditional recommendation against the option ○	Conditional recommendation for either the option or the comparison ○	Conditional recommendation for the option ○	Strong recommendation for the option ○
RECOMMENDATION	Recommendation: Recommendation 1: For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol) interventions should be considered in accordance with the WHO mhGAP guidelines. (<i>Strength of recommendation: Conditional; Quality of the evidence: Low</i>). Recommendation 2: Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with SMD and substance use disorders (<i>Strength of recommendation: Conditional; Quality of the evidence: Very low</i>). Best practice statement: Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and SMD. Additional considerations: ▪ Certain side effects (somnolence, hypersalivation, and constipation) may be more prevalent in people treated with clozapine, which should be a consideration when determining choice of pharmacotherapy. ▪ People with SMD who are injecting drug users may be at an increased risk of Hepatitis B and C through the sharing of contaminated instruments and/ or needles. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and				

	Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA. (https://www.cdc.gov/hepatitis/populations/idu.htm).
JUSTIFICATION	Detailed reviews revealed low to very low quality evidence from randomized controlled trials, which did not support the superiority of any of the pharmacological interventions against each other, or any of the psychosocial interventions against each other in populations with dual diagnoses. None of the reviewed trials for psychosocial therapies have been conducted in low and middle income country settings. The absence of high quality evidence does not mean that these treatments do not work but that at present the evidence is of insufficient quality to support the use of one form of non-pharmacological or psychosocial intervention over another in these special populations. For substance use-related outcomes (levels of consumption, frequency of use, abstinence and relapse rates) in people with SMD: 1. Detailed reviews indicate little evidence to support the superiority of one antipsychotic medication over another. Certain side effects (somnolence, hypersalivation, and constipation) may be more prevalent in people treated with Clozapine, which should be a consideration when determining choice of pharmacotherapy. NB. Only Risperidone and Clozapine are included on the WHO Essential Medications List) 2. There was some evidence to indicate motivational interviewing for cannabis use and alcohol use may be effective in dual diagnoses populations. There was one study from reviews which suggested contingency management for substance use may be beneficial.
SUBGROUP CONSIDERATIONS	▪ People with SMD who are injecting drug users may be at an increased risk of Hepatitis B and C through the sharing of contaminated instruments and/ or needles. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with severe mental disorders who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been

	recommended by the CDC (https://www.cdc.gov/hepatitis/populations/idu.html), USA.
IMPLEMENTATION CONSIDERATIONS	Note that Methadone and Buprenorphine have major interactions with many commonly used psychotropic medications
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	1. Better quality, adequately powered studies of pharmacological interventions in people with dual diagnoses (severe mental illnesses comorbid with substance misuse), which are conducted preferably over multi-site locations, and include people who misuse a range of substances including polysubstance misuse. 2. Better quality, adequately powered studies which assess whether specific psychosocial interventions benefit people with dual diagnoses for outcomes such as drug and alcohol abstinence, drug/ alcohol consumption and impact on mental state, retention and relapse rates, particularly over the longer-term (longer than 6-12 months), are needed. Interventions which may show promise include contingency management for injecting drug use and motivational interviewing for cannabis and alcohol use in the short-term. At present evidence relating to the superiority of these therapies is of low/ very low certainty to inform recommendations. 3. Studies which assess the implementation of interventions for dual diagnoses in low and middle income country settings. 4. Studies which address cost effectiveness as well as clinical efficacy (for 1-2).

Remarks

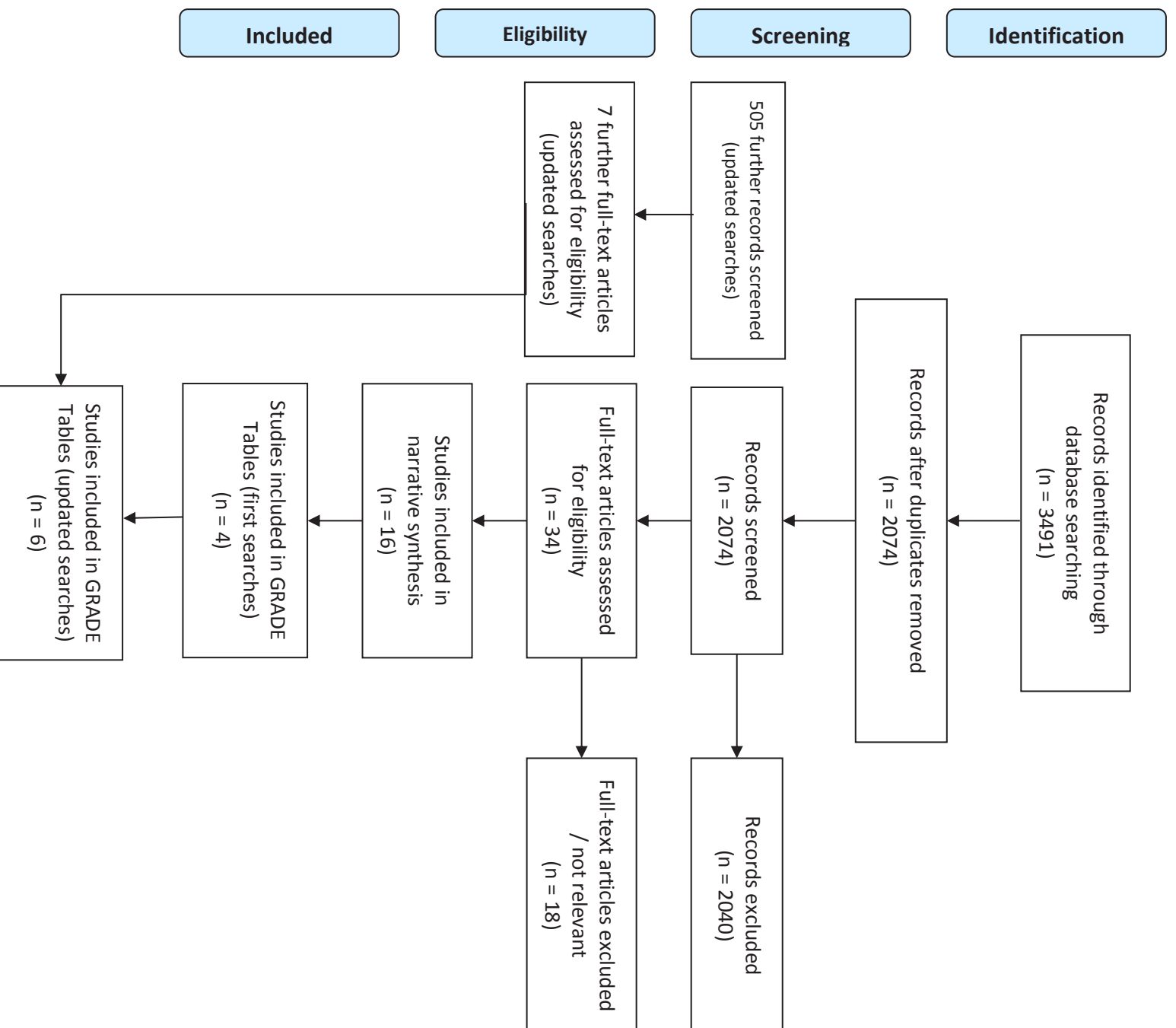
- All of the evidence comes from high-income countries. All of the evidence had an overall rating of very low to low.

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PRISMA Flow Diagram for systematic review of the reviews: SMD and substance use disorders



EVIDENCE PROFILE
CARDIOVASCULAR DISEASE & CARDIOVASCULAR RISK

PICO QUESTIONS:

5.1 For people with severe mental disorder (SMD) and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

5.2 For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Background on the PICO question

The majority of deaths amongst people with SMD are attributable to physical diseases. Cardiovascular disease is considered a main potentially avoidable contributor to excess mortality observed amongst people with SMD, with a ten-fold higher risk of death than suicide amongst the same population. Overall, people with SMD have an approximately 1.5-3 times higher risk of cardiovascular morbidity and mortality compared to the general population.

This increased risk of death due to circulatory diseases is well documented, especially among persons with schizophrenia. Among those with any SMD, the HRs for coronary heart disease mortality was high across all age groups compared with controls: 3.22 (95% CI, 1.99-5.21) for those between the ages of 18-49 years, 1.86 (95%CI, 1.63-2.12) for those between the ages of 50-75 years, and 1.34 (95% CI, 1.17-1.54) for those older than 75 years (Osborn et al., 2007). In schizophrenia, cardiovascular disease is the single largest cause of death (Colton & Manderscheid, 2006) and major cause of excess premature mortality (Laursen 2011). Up to 75% of patients with schizophrenia (compared to about 33% of the general population) die of coronary heart disease (Henekens et al., 2005). In schizophrenia, most studies report an RR for death due to circulatory diseases around 2- to 3-fold compared to those without schizophrenia (Laursen et al., 2013). In Sweden, there was a 2.42-fold (aHR, 95% CI, 2.12-2.77) risk for men and 2.94-fold (aHR, 95% CI, 2.56-3.37) risk for women of dying from cardiovascular disease compared to the general population (Crump, Winkleby et al., 2013). Comparing those with schizophrenia who died of heart conditions versus those in the general population who also died of heart conditions from 3 Nordic countries, persons with schizophrenia had a two to three-fold risk of dying from cardiovascular disease (Laursen et al., 2013). In Israel, persons with schizophrenia with a diagnosis of cardiovascular disease had a 2.3-fold risk for death compared with those without schizophrenia (aHR=2.29, 95% CI, 2.10-2.50) (Gal et al., 2015). Among persons with schizophrenia who died from ischemic heart disease, women died 12.5 years earlier and men

died 14.5 years earlier than other women and men without schizophrenia (Crump, Winkleby et al., 2013). This cannot be explained by lifestyle factors alone: after adjusting for smoking and other substance abuse disorder, death due to ischemic heart disease only decreased minimally: for women from 3.33 (95% CI, 2.73-4.05) to 3.28 (95% CI, 2.70-4.00) and for men from 2.20 (95% CI, 1.83-2.65) to 2.11 (95% CI, 1.75-2.54) (Crump, Winkleby et al., 2013).

In bipolar disorder, the risk of death by circulatory disease is about twice as high compared to the general population (Westman et al., 2013). A systematic review of deaths from circulatory disease in persons with bipolar disorder found an SMR of 1.73 (95%CI 1.54 – 1.94) (Hayes et al., 2015). Similarly, data from Nordic countries found a two-fold risk of death due to circulatory diseases in all countries for both sexes (Laursen et al., 2013). Persons with bipolar disorder died of cardiovascular disease approximately 10 years earlier than the general population (Westman et al., 2013).

Persons with depression have a 1.5-2.0 times higher risk of dying from circulatory diseases compared to the general population. Data from the Global Burden of Disease showed that the pooled RR risk of developing ischemic heart disease in those with depression was 1.56 (95% CI, 1.30-1.87) (Charlson et al., 2013). The relationship between depression and circulatory disease appears to be bidirectional: persons with depression are twice as likely to have a heart attack as the general population (Rugulies et al., 2002) and depression further increases the risk of death in patients with cardiac disease (Whang et al., 2010). In a systematic review, compared with other heart disease patients, persons with comorbid depression had a 1.72 (95% CI, 1.56-1.90) greater RR of dying compared to other heart disease patients (Cuijpers et al., 2014). In a 15-year population-based study of young people (mean age=28.1 years) that controlled for socioeconomic status, lifestyle factors and comorbid medical conditions, the PAR for ischemic heart disease in women with depression and a history of an attempted suicide was more than any traditional risk factor for ischemic heart disease (i.e., smoking, hypertension, diabetes mellitus, and obesity) (Shah et al., 2011). Further, the severity level of depression appears associated with an incremental increased risk of circulatory problems among persons with depression (Almas et al., 2015; Wei et al., 2014).

In LMICs, circulatory disease deaths also appear common among persons with SMD: in rural China, 7 of 42 (16.7%) known death cases of those with schizophrenia in a 10-year cohort study were due to heart disease (Ran et al., 2007); however detailed data about deaths due to circulatory diseases are more limited from LAMICs and not reported in some settings, likely due to the few deaths attributed to this (e.g., Fekadu et al., 2015).

This document covers evidence regarding pharmacological and/or non-pharmacological interventions for cardiovascular diseases and risk factors amongst people with SMD. Those outcomes have been included that were considered to be critical or important to this population group.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Cardiovascular disease

Population: people with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

Intervention: pharmacological and/or non-pharmacological interventions

Comparison: one treatment versus another or care as usual / placebo

Outcomes:

- Critical
 - o Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important:
 - o Frequency of adverse events/side-effects

Cardiovascular risk

Population: people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels)

Intervention: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

Comparison: one treatment versus another or care as usual / placebo

Outcomes:

- Critical
 - o Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)

- Cardiovascular disease incidence
- Important:
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

De Silva VA et al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

also see: Gierisch JM et al. Pharmacologic and Behavioral Interventions to Improve Cardiovascular Risk Factors in Adults With Serious Mental Illness: A Systematic Review and Meta-Analysis. J Clin Psychiatry 2014;75(5):e424–e440

Maslej MM et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. Psychotherapy and Psychosomatics. 2017; 86(5): 268-282

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Nieuwsma JA et al. Diagnostic accuracy of screening tests and treatment for post-acute coronary syndrome depression. Annals of Internal Medicine. 2017; 167(10): 725-735

Ski CF et al. Psychosocial interventions for patients with coronary heart disease and depression: A systematic review and meta-analysis. European Journal of Cardiovascular Nursing. 2016; 15(5): 305-316

Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18

Tully J & Baumeister H. Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2015; 5(12): e009128

Verschueren S et al. The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease: A systematic review. *Journal of Psychosomatic Research*. 2018; 105: 80-91

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Agarwal M et al. Pharmacological interventions for reduction or prevention of weight gain in schizophrenia: A cochrane meta-analysis. *Neuropsychopharmacology*. 2017; 43(1): s612-s613

Bai XL et al. Effectiveness and safety of Wuling capsule for post stroke depression: A systematic review. *Chinese Journal of Evidence-Based Medicine*. 2014; 14(9): 1104-1111

Bauer IE et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: A systematic review. *Journal of Psychiatric Research*. 2016; 74: 1-7

Baxter AJ et al. Reducing excess mortality due to chronic disease in people with severe mental illness: Meta-review of health interventions. *British Journal of Psychiatry*. 2016; 208(4)

Bisogni V et al. Antihypertensive therapy in patients affected by bipolar disorders treated with lithium: A systematic review. *Journal of Hypertension*. 2015; 1: e459

Brasier C et al. Effectiveness of psychosocial interventions on stroke survivors, their carers and stroke-carer dyads. *International Journal of Stroke*. 2017; 12 (2 S1): 27

Bruins J et al. The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: a meta-analysis. *PLOS One*. 2014; 9(12): e112276

Chalfoun C et al. Running for your life: A review of physical activity and cardiovascular disease risk reduction in individuals with schizophrenia. *J Sports Sci*. 2016; 34(16): 1500-1515

Cooper SJ et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol*. 2016; 30(8): 717-48

Correll CU et al. Selective effects of individual antipsychotic cotreatments on cardiometabolic and hormonal risk status: Results from a systematic review and meta-analysis. *Schizophrenia Bulletin*. 2013; 1: S29-S30

Deng L et al. Interventions for management of post-stroke depression: A bayesian network meta-analysis of 23 randomized controlled trials. *Journal of the Neurological Sciences*. 2017; 381 (Supplement 1): 163-164

- Dickens C et al. Characteristics of psychological interventions that improve depression in people with coronary heart disease: a systematic review and meta-regression (Structured abstract). *Psychosomatic Medicine*. 2013; 75(2):211-221
- Dwyer Hollender K. Screening, diagnosis, and treatment of post-stroke depression. *Journal of Neuroscience Nursing*. 2014. 46(3):135–141
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- Jeyanantham K et al. Effects of cognitive behavioural therapy for depression in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*. 2017; 22(6): 731-741
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- Lally J et al. Pharmacological interventions for clozapine-induced sinus tachycardia. *Cochrane Database of Systematic Reviews*. 2016; 6
- Lawrence M et al. A systematic review of the benefits of mindfulness-based interventions following transient ischemic attack and stroke. *International Journal of Stroke*. 2013; 8(6): 465-474
- Liu Z et al. Metformin for treatment of clozapine-induced weight gain in adult patients with schizophrenia: A meta-analysis. *Shanghai Archives of Psychiatry*. 2015; 27(6): 331-340
- Lucenteforte E et al. Inappropriate pharmacological treatment in older adults affected by cardiovascular disease and other chronic comorbidities: A systematic literature review to identify potentially inappropriate prescription indicators. *Clinical Interventions in Aging*. 2017; 12: 1761-1778
- Maia ACCO et al. Efficacy of cognitive behavioral therapy in reducing psychiatric symptoms in patients with implantable cardioverter defibrillator: An integrative review. *Brazilian Journal of Medical and Biological Research*. 2014; 47(4): 265-272
- Matcham F et al. Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illnesses: A systematic review and meta-analysis. *Clinical Psychology Review*. 2014; 34(2): 141-157
- McIntyre A et al. Repetitive Transcranial Magnetic Stimulation for Depression Due to Cerebrovascular Disease: A Systematic Review. *Journal of Stroke and Cerebrovascular Diseases*. 2016; 25(12): 2792-2800

Mead GE et al. Selective serotonin reuptake inhibitors for stroke recovery: A systematic review and meta-analysis. Sao Paulo Medical Journal. 2013; 131(3): 208

Also in: Stroke. 2013; 44(3): 844-850

Nielsen et al. Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? Journal of Clinical Psychiatry. 2013; 74(6): 603-613

Peng L et al. Effectiveness and safety of Wuling capsule for post stroke depression: A systematic review. Complementary Therapies in Medicine. 2014; 22(3): 549-566

Protopogerou C et al. Moderators of the effect of psychological interventions on depression and anxiety in cardiac surgery patients: A systematic review and meta-analysis. Behaviour Research and Therapy. 2015; 73: 151-164

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Ramamurthy G et al. Depression treatment in patients with coronary artery disease: A systematic review. Primary Care Companion to the Journal of Clinical Psychiatry. 2013; 15(5)

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Richards SH et al. Psychological interventions for coronary heart disease. Cochrane Database of Systematic Reviews. 2017; 4

Rustad JK et al. Diagnosis and treatment of depression in patients with congestive heart failure: A review of the literature. Primary Care Companion to the Journal of Clinical Psychiatry. 2013; 15(4)

Rutledge T et al. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. Psychosomatic Medicine. 2013; 75(4): 335-349

Samartzis L et al. SSRIs versus exercise training for depression in chronic heart failure: A meta-analysis of randomized controlled trials. 2013; 168(5): 4956-4958

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Shulman L et al. Managing cardiovascular disease risk in patients treated with antipsychotics: A multidisciplinary approach. Journal of Multidisciplinary Healthcare. 2014; 7: 489-501

- Smith SM et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev*. 2016; 3: CD006560-CD006560
- Thayabaranathan T et al. Determining the potential benefits of yoga in chronic stroke care: A systematic review and meta-analysis. *Topics in Stroke Rehabilitation*. 2017; 24(4): 279-287
- Thombs TB et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. *Plos One*. 2013; 8(1): e52654
- Thompson D et al. Psychological interventions for patients with coronary heart disease and their partners: A systematic review. *Cardiology*. 2013; 13(2): 173
- Thompson SR et al. Treatment of vascular depression and post stroke depression using repetitive transcranial magnetic stimulation: Systematic review. *Archives of Physical Medicine and Rehabilitation*. 2015; 96(10): e118
- Tu RH et al. Effects of exercise training on depression in patients with heart failure: A systematic review and meta-analysis of randomized controlled trials. *European Journal of Heart Failure*. 2014; 16(7): 749-757
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- van Eck van der Sluijs JF et al. Illness burden and physical outcomes associated with collaborative care in patients with comorbid depressive disorder in chronic medical conditions: A systematic review and meta-analysis. *General Hospital Psychiatry*. 2018; 50: 1-14
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- Whiteman KL et al. Systematic review of integrated general medical and psychiatric self-management interventions for adults with serious mental illness. *Psychiatric Services*. 2016; 67(11): 1213-1225
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PICO Tables

Cardiovascular disease

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Antidepressants vs. care as usual (1)	Major adverse cardiovascular event (MACE)	Maslej MM et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. <i>Psychotherapy and Psychosomatics</i> . 2017; 86(5): 268-282	One of two most recent high-quality systematic review on antidepressants in people with CVD and depression (rather than SMD overall, as this was not available).
		Frequency of adverse events/side-effects		
2	Antidepressants vs. care as usual (2)	Major adverse cardiovascular event (MACE)	Nieuwsma JA et al. Diagnostic accuracy of screening tests and treatment for post-acute coronary syndrome depression. <i>Annals of Internal Medicine</i> . 2017; 167(10): 725-735	One of two most recent high-quality systematic review on antidepressants in people with CVD and depression (rather than SMD overall, as this was not available).
		Frequency of adverse events/side-effects		
3	Psychosocial interventions vs. care as usual	Major adverse cardiovascular event (MACE)	Ski CF et al. Psychosocial interventions for patients with coronary heart disease and depression: A systematic review and meta-analysis. <i>European Journal of Cardiovascular Nursing</i> . 2016; 15(5): 305-316	The most recent high-quality systematic review on psychosocial interventions generally, but for depression only (as no systematic review available for SMD).
		Frequency of adverse events/side-effects		
4	Exercise therapy vs. care as usual	Major adverse cardiovascular event (MACE)	Verschuere S et al. The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease: A systematic review. <i>Journal of</i>	The most recent high-quality systematic review on exercise therapy, but for depression only (as no systematic review
		Frequency of adverse		

		events/side-effects	Psychosomatic Research. 2018; 105: 80-91	available for SMD).
5	Collaborative care vs. care as usual	Major adverse cardiovascular event (MACE)	Tully J & Baumeister H. Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2015; 5(12): e009128	The most recent high-quality systematic review on collaborative care, but for depression only (as no systematic review available for SMD).
		Frequency of adverse events/side-effects		
	Pharmacological interventions vs. another treatment	Major adverse cardiovascular event (MACE)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects		
	Non-pharmacological interventions vs. another treatment	Major adverse cardiovascular event (MACE)	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects		

Cardiovascular risk

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
6	Metformin vs. placebo	Adequacy of control of CVD risk factors – blood pressure	No relevant systematic review available.	N/A
		Adequacy of control of CVD risk factors – cholesterol	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent comprehensive high-quality systematic review (meta- analysis) available for people with SMD for this outcome.
		Cardiovascular disease incidence	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016: 16(1): 341	Most recent high-quality systematic review (meta-analysis) available for people with SMD for this outcome.
7	Aripiprazole vs. placebo	Adequacy of control of CVD risk factors – blood pressure	No relevant systematic review available.	N/A
		Adequacy of control of CVD risk factors – cholesterol	Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403	Most recent comprehensive high-quality systematic review (meta- analysis) available for people with SMD for this outcome.
		Cardiovascular disease	No relevant systematic review available.	N/A

		incidence		
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013 (also see: Gierisch JM et al. Pharmacologic and Behavioral Interventions to Improve Cardiovascular Risk Factors in Adults With Serious Mental Illness: A Systematic Review and Meta-Analysis. J Clin Psychiatry 2014;75(5):e424–e440)	Most recent high-quality comprehensive systematic review (meta- analysis) available for people with SMD for this outcome.
8	Lifestyle interventions vs. care as usual	Adequacy of control of CVD risk factors – blood pressure	Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18	Most recent high-quality comprehensive systematic review (meta- analysis) available for people with SMD for this outcome.
		Adequacy of control of CVD risk factors – cholesterol	Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18	Most recent high-quality comprehensive systematic review (meta- analysis) available for people with SMD for this outcome.
		Cardiovascular disease incidence	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013 (also see: Gierisch JM et al. Pharmacologic and Behavioral Interventions to Improve Cardiovascular Risk Factors in Adults With Serious Mental Illness: A Systematic Review and Meta-Analysis. J Clin Psychiatry	Most recent high-quality comprehensive systematic review (meta- analysis) available for people with SMD for this outcome.

			2014;75(5):e424–e440)	
	Pharmacological interventions vs. another treatment	Adequacy of control of CVD risk factors – blood pressure Adequacy of control of CVD risk factors – cholesterol Cardiovascular disease incidence Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
	Non-pharmacological interventions vs. another treatment	Adequacy of control of CVD risk factors – blood pressure Adequacy of control of CVD risk factors – cholesterol Cardiovascular disease incidence Frequency of adverse events/side-effects	No relevant systematic review available.	N/A

Narrative description of the studies that went into analysis¹

Cardiovascular disease

Maslej et al (2017) conducted a meta-analysis assessing the effects of ADs on all-cause mortality and cardiovascular events in general-population and cardiovascular-patient samples. Methods: Two reviewers independently assessed articles from PubMed, EMBASE, and Google Scholar for AD-related mortality controlling for depression and other comorbidities. From these articles, the authors extracted information about cardiovascular events, cardiovascular risk status, and AD class. They conducted mixed-effect meta-analyses testing sample type and AD class as moderators of all-cause mortality and new cardiovascular events. Results: Seventeen studies met the search criteria. Sample type consistently moderated health risks. In general-population samples, AD use increased the risks of mortality (HR = 1.33, 95% CI: 1.14-1.55) and new cardiovascular events (HR = 1.14, 95% CI: 1.08-1.21). In cardiovascular patients, AD use did not significantly affect risks. AD class also moderated mortality, but the serotonin reuptake inhibitors were not significantly different from tricyclic ADs (TCAs) (HR = 1.10, 95% CI: 0.93-1.31, $p = 0.27$). Only 'other Ads' were differentiable from TCAs (HR = 1.35, 95% CI: 1.08-1.69). Mortality risk estimates increased when they analyzed the subset of studies controlling for premedication depression, suggesting the absence of confounding by indication. Conclusions: The results support the hypothesis that ADs are harmful in the general population but less harmful in cardiovascular patients.

Nieuwsma et al (2017) conducted a meta-analysis, to evaluate the diagnostic accuracy of depression screening instruments and to compare safety and effectiveness of depression treatments in adults within 3 months of an ACS event. Data Sources: MEDLINE, EMBASE, PsycINFO, CINAHL, and Cochrane Database of Systematic Reviews from January 2003 to August 2017, and a manual search of citations from key primary and review articles. Study Selection: English-language studies of post-ACS patients that evaluated the diagnostic accuracy of depression screening tools or compared the safety and effectiveness of a broad range of pharmacologic and nonpharmacologic depression treatments. Data Extraction: 2 investigators independently screened each article for inclusion; abstracted the data; and rated the quality, applicability, and strength of evidence. Data Synthesis: Evidence from 6 of the 10 included studies showed that a range of depression screening instruments produces acceptable levels of diagnostic sensitivity, specificity, and negative predictive values (70% to 100%) but low positive predictive values (below 50%). The Beck Depression Inventory-II was the most studied tool. A large study found that a combination of cognitive behavioral therapy (CBT) and antidepressant medication improved depression symptoms, mental health-related function, and overall life satisfaction more than usual care. Limitation: Few studies, no evaluation of the influence of screening on clinical outcomes, and no studies addressing several clinical interventions of interest. Conclusion: Depression screening instruments produce diagnostic accuracy metrics that are similar in post-ACS patients and other clinical populations. Depression interventions have an uncertain effect on cardiovascular outcomes, but CBT combined with antidepressant medication produces modest improvement in psychosocial outcomes.

¹ Please note that this section includes the abstracts as taken directly from the publications.

Ski et al 2016 conducted a meta-analysis review aimed to assess the effectiveness of psychosocial interventions addressing both depression and social support for people with coronary heart disease and depression. Methods: PRISMA guidelines were used to search major health databases to identify randomised controlled trials that evaluated psychosocial interventions compared with usual care in patients with coronary heart disease and depression; the primary outcome was depressive symptoms and secondary outcomes were mortality (all-cause and cardiac), myocardial infarction, revascularisation, anxiety, social support and quality of life. Data, when suitable, were pooled using a random-effects meta-analysis model. Results: Five studies (n=1358 participants) were eligible and included. The psychosocial intervention group had significantly lower levels of depressive symptoms (standardised mean difference (SMD) -0.15, 95% confidence interval (CI) -0.27 to -0.03; P=0.02) and higher levels of social support (SMD 0.17; 95% CI 0.04 to 0.30; P=0.01) but no differences were found for mortality (all-cause and cardiac), myocardial infarction, revascularisation, anxiety or quality of life. Conclusions: Psychosocial interventions for patients with coronary heart disease and depression result in modest reductions in depressive symptoms and improvements in social support. However, caution is warranted in view of the small number of studies included in the review and potential heterogeneity in outcomes and in differences in treatment.

Tully & Baumeister (2015) aimed to assess the efficacy of collaborative care (CC) for depression in adults with coronary heart disease (CHD) and depression. Design: Systematic review and meta-analysis. Data sources: Electronic databases (Cochrane Central Register of Controlled Trials MEDLINE, EMBASE, PsycINFO and CINAHL) were searched until April 2014. Inclusion criteria: Population, depression comorbid with CHD; intervention, randomised controlled trial (RCT) of CC; comparison, either usual care, wait-list control group or no further treatment; and outcome, (primary) major adverse cardiac events (MACE), (secondary) standardised measure of depression, anxiety, quality of life (QOL) and cost-effectiveness. Results: Six RCTs met the inclusion criteria and comprised 655 participants randomised to CC and 629 participants randomised to the control group (total 1284). Collaborative depression care led to a significant reduction in MACE in the short term (three trials, RR 0.54; 95% CI 0.31 to 0.95, p=0.03) that was not sustained in the longer term. Small reductions in depressive symptoms were evident in the short term (6 trials, pooled SMD -0.31; 95% CI -0.43 to -0.19, p<0.00001) and depression remission was more likely to be achieved with CC (5 trials, OR 1.77; 95% CI 1.28 to 2.44, p=0.0005). Likewise, a significant effect was observed for anxiety symptoms (SMD -0.36) and mental QOL (SMD 0.24). The timing of the intervention was a source of between-group heterogeneity for depression symptoms (between groups p=0.04, I²=76.5%). Conclusions: Collaborative depression care did not lead to a sustained reduction in the primary MACE end point. Small effects were observed for depression, depression remission, anxiety and mental QOL.

Verschueren et al (2018) systematically reviewed the existing literature on the effectiveness of exercise therapy to reduce depression and anxiety symptoms specifically in patients with ischemic heart disease (IHD). Methods MEDLINE, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials were searched until January 2016. The effectiveness of exercise was assessed within two groups: a) patients selected for study with severe depression or anxiety; and b) studies that did not exclusively targeted patients with increased levels of depression or anxiety. Secondary outcomes were mortality, cardiac events, re-hospitalizations and cardiovascular risk factors. Results: Fourteen studies were included. Clinical and methodological heterogeneity precluded meta-analysis. Three studies specifically included patients with high levels of depression or anxiety and eleven studies selected patients with unclear levels of depression or anxiety. Some RCTs showed that exercise was effective in lowering severe depressive symptoms (short and long term follow-up), but for the group with unclear depressive symptoms the results were non-conclusive. In the group with

elevated anxiety symptoms, exercise had a positive effect on the short term follow-up. In the group with unclear anxiety symptoms the results were inconsistent (short and long term follow-up). No differences were found regarding the secondary outcomes. Conclusions: There is a general paucity of data on the effect of exercise, precluding firm conclusions about the effectiveness of exercise in IHD patients.

Cardiovascular risk

Mizuno et al (2014) conducted a meta-analysis to systematically determine the effectiveness of medications to counteract antipsychotic-induced metabolic adversities in patients with schizophrenia. Double-blind randomized placebo-controlled trials focusing on patients with schizophrenia were included if they evaluated the effects of concomitant medications on antipsychotic-induced metabolic adversities as a primary outcome. Forty trials representing 19 unique interventions were included in this meta-analysis. Metformin was the most extensively studied drug in regard to body weight, the mean difference amounting to -3.17 kg (95% CI: -4.44 to -1.90 kg) compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also different from placebo. Furthermore, metformin and rosiglitazone improved insulin resistance, while aripiprazole, metformin, and sibutramine decreased blood lipids. Author's conclusions: When nonpharmacological strategies alone are insufficient, and switching antipsychotics to relatively weight-neutral agents is not feasible, the literature supports the use of concomitant metformin as first choice among pharmacological interventions to counteract antipsychotic-induced weight gain and other metabolic adversities in schizophrenia.

De Silva et al (2016) conducted a systematic review to assess the efficacy of metformin in the treatment of antipsychotic induced weight gain. Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE were searched for the period January 2000-December 2015. Meta-analysis was carried out using the random effects model. Meta-analysis of 12 published studies with a total of 743 patients found that in patients treated with antipsychotics, metformin treatment resulted in significantly better anthropometric and metabolic parameters than placebo. The mean change in weight was -3.27 kg (95 % CI -4.66 to -1.89) ($Z = 4.64$, $p < 0.001$). Metformin compared to placebo resulted in significant reduction in BMI [-1.13 kg/m² (95 % CI -1.61 to -0.66)] and insulin resistance index [-1.49 (95 % CI -2.40 to -0.59)] but not fasting blood sugar [-2.48 mg/dl (95 % CI -5.54 to 0.57)]. Authors' conclusions: This meta-analysis confirms that metformin is effective in treating antipsychotic induced weight gain in patients with schizophrenia or schizoaffective disorder.

Gierisch (2013, 2014) conducted a systematic review to evaluate interventions to improve CVD risk factors in adults with SMD. Of 35 eligible studies, most enrolled patients with schizophrenia who were prescribed antipsychotics. Most studies were designed to control weight ($n=28$); one study specifically addressed diabetes management, none targeted hyperlipidemia, and three were multicondition interventions. Most studies were efficacy trials comparing behavioral interventions with control; none evaluated peer and family support. There were few direct comparisons of active interventions; effects on overall CVD risk, physical functioning, or cardiovascular events were reported rarely. Compared with controls, behavioral interventions (mean difference [MD] -3.13 kg; 95% CI, -4.21 to -2.05), metformin (MD -4.13 kg; CI, -6.58 to -1.68), the anticonvulsive medications topiramate and zonisamide (MD -5.11kg; CI, -9.48 to -0.74), and adjunctive or antipsychotic switching to aripiprazole improved weight control. However, aripiprazole switching may be associated with higher rates of treatment failure. Nizatidine did not improve any outcome. The evidence was insufficient for all other interventions and effects on glucose and lipid control. Authors' conclusions: Few studies have evaluated interventions to

address one or more CVD risk factors in patients with SMD. Comparative effectiveness studies are needed to test multimodal strategies, agents known to be effective in non-SMI populations, and antipsychotic-management strategies.

Teasdale et al (2017) subjected randomised controlled trials of nutrition interventions in people with SMD to systematic review and meta-analysis, and measured anthropometric and biochemical parameters and nutritional intake. Meta-regression analyses were performed on anthropometric moderators. Interventions led to significant weight loss (19 studies), reduced body mass index (17 studies), decreased waist circumference (10 studies) and lower blood glucose levels (5 studies). Dietitian-led interventions (6 studies) and studies delivered at antipsychotic initiation (4 studies) had larger effect sizes. Authors' conclusions: Evidence supports nutrition interventions as standard care in preventing and treating weight gain among people experiencing SMI.

GRADE Evidence Tables²

Cardiovascular disease

Table 1: Antidepressants vs. care as usual for people with SMD and cardiovascular disease (1)

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Antidepressants compared to no antidepressants for people with SMD and cardiovascular disease

Setting: inpatients and outpatients

Bibliography: Maslej MM et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. *Psychotherapy and Psychosomatics*. 2017; 86(5): 268-282

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	antidepressants	care as usual	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (MACE) (HR below 1 favours antidepressants)												
11 ^a	observational studies ^b	serious ^c	not serious ^d	very serious ^e	not serious	none detected ^f	N/A	N/A	HR 0.93 (0.82 to 1.06)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ VERY LOW	CRITICAL
Frequency of adverse events / side-effects (HR below 1 favours antidepressants)												
11 ^a	observational studies ^b	serious ^c	very serious ^g	very serious ^e	not serious	none detected ^f	N/A	N/A	HR 0.90 (0.76 to 1.07)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. The systematic review (Maslej et al 2017) included and contrasted studies in the general population and participants with cardiovascular disease. Only the latter group of studies is presented in the table here. Participants in included studies had heart failure (n=4), acute coronary syndrome (n=2),

² See Annex 5, page XX for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

- coronary angiography (n=1), COPD (n=1), coronary heart disease (n=1), chronic kidney disease (n=1), and veterans at high risk of cardiovascular disease (n=1).
- b. 10 of the studies had a cohort design and 1 study was an RCT (cited in Maslej et al 2017).
 - c. This has been rated as serious, as only 1 of the studies was randomised, and 1 study had an unclear risk of bias for attrition bias. This information was taken from Supp 5.2 & 6.1 in Maslej et al 2017.
 - d. This has been rated as not serious, as heterogeneity (I²) was reported to be 26% by Maslej et al 2017. (see page 273).
 - e. This has been rated as very serious, as the systematic review did not specify what reason the antidepressants were taken for, i.e. whether participants had depression or were taking the antidepressants for another reason, and also did not specifically include people with SMD.
 - f. The authors of the systematic review (Maslej et al 2017) produced funnel plots, which showed no bias. See Supp material B1 in Maslej et al 2017.
 - g. This has been rated as very serious, as heterogeneity (I²) was reported to be 87% by Maslej et al 2017 (see page 273).

Table 2: Antidepressants vs. care as usual for people with SMD and post-acute coronary syndrome (2)

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Antidepressants compared to care as usual for people with SMD and post-acute coronary syndrome

Setting: cardiovascular inpatients in hospital

Bibliography: Nieuwsma JA et al. Diagnostic accuracy of screening tests and treatment for post-acute coronary syndrome depression. *Annals of Internal Medicine*. 2017; 167(10: 725-735

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	antidepressants	care as usual	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (MACE) (OR below 1 favours antidepressants) (follow up: 18 months)												
1 ^a	randomised trials	not serious	not serious	serious ^b	very serious ^c	none detected ^d	-/209	-/122	OR 1.07 (0.57 to 2.00)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
Frequency of adverse events / side-effects (OR below 1 favours antidepressants) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. The systematic review (Nieuwsma et al 2017) found only 1 study. The study included participants who were hospitalised for acute myocardial infarction and were diagnosed with comorbid major depressive disorder in the Netherlands.

b. This has been rated as serious, as participants had depression rather than SMD overall.

c. This has been rated as very serious, as the confidence interval includes both 'no effect' and appreciable harm, and evidence comes from just 1 study. See Table 3 in Nieuwsma et al 2017.

d. Publication bias was not detected by the authors, though funnel plots were not produced due to the low number of studies. See Table 3 in Nieuwsma et al 2017.

Table 3: Psychosocial interventions vs. care as usual for people with SMD and cardiovascular disease

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Psychosocial interventions compared to care as usual for people with SMD and pre-existing cardiovascular disease

Setting: inpatients and outpatients

Bibliography:

Ski CF et al. Psychosocial interventions for patients with coronary heart disease and depression: A systematic review and meta-analysis. European Journal of Cardiovascular Nursing. 2016; 15(5): 305-316

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	psychosocial interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (MACE) - cardiovascular mortality (RR below 1 favours psychosocial interventions) (follow up: mean 29 months)												
1 ^a	randomised trials	not serious ^b	not serious ^c	serious ^d	serious ^e	none detected ^f	-/498	-/480	RR 0.92 (0.57 to 1.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
Major adverse cardiovascular event (MACE) - myocardial infarction (RR below 1 favours psychosocial interventions)												
2 ^g	randomised trials	not serious ^b	not serious ^h	serious ^d	serious ^e	none detected ^f	69/569 (12.1%)	62/571 (10.9%)	RR 1.12 (0.81 to 1.53)	13 more per 1,000 (from 21 fewer to 58 more)	⊕⊕○○ LOW	CRITICAL
Major adverse cardiovascular event (MACE) - revascularisation (RR below 1 favours psychosocial interventions) (follow up: mean 29 months)												
1 ^a	randomised trials	not serious ^b	not serious ^c	serious ^d	not serious	none detected ^f	-/498	-/480	RR 0.97 (0.73 to 1.29)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Frequency of adverse events / side-effects - all-cause mortality (RR below 1 favours psychosocial interventions) (follow up: mean 29 months)												
1 ^a	randomised trials	not serious ^b	not serious ^c	serious ^d	not serious	none detected ^f	-/498	-/480	RR 0.97 (0.67 to 1.39)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. The systematic review (Ski et al 2016) found only 1 relevant study.. The study entailed weekly CBT sessions over 1.5 to 9 months in patients with myocardial infarction and depression (either MDD, minor depression or dysthymia) in the USA.
- b. The authors of the systematic review (Ski et al 2016) reported randomization for the included study/studies, that outcome assessment had been masked, and low risk of bias for attrition. See page 310 in Ski et al 2016.
- c. This has been rated as not serious, though only one study was included, so heterogeneity is not relevant/appropriate here.
- d. This has been rated as serious, as the study included participants with depression rather than SMD overall.
- e. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable benefit and harm.
- f. Publication bias was not assessed by the authors of the systematic review (Ski et al 2016), so was not detected.
- g. The 2 included studies by Ski et al 2016 were as follows Weekly CBT sessions over 1.5 to 9 months in patients with myocardial infarction and depression; USA. Weekly interpersonal psychotherapy plus clinical management over 3 months for people with major depression and either myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, either in person or by phone; Canada.
- h. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Ski et al 2016 (see Figure 3).

Table 4: Exercise therapy vs. care as usual for people with SMD and cardiovascular disease

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Exercise therapy compared to care as usual or comparator intervention for people with SMD and cardiovascular disease

Setting: inpatients and outpatients

Bibliography: Verschueren S et al. The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease: A systematic review. Journal of Psychosomatic Research. 2018; 105: 80-91

systematic review. Journal of Psychosomatic Research. 2016; 100: 66-81

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	exercise therapy	care as usual or comparator intervention	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (MACE) (RR below 1 favours exercise therapy) (follow up: 12 weeks)												
1 ^a	randomised trials	serious ^b	not serious ^c	serious ^d	very serious ^e	none detected ^f	1/42 (2.4%)	4/35 (11.4%)	RR 0.69 (0.04 to 10.60)	35 fewer per 1,000 (from 110 fewer to 1,000 more)	⊕○○○ VERY LOW	CRITICAL
Frequency of adverse events / side-effects - mortality (RR below 1 favours exercise therapy)												
2 ^g	randomised trials	serious ^b	serious ^h	serious ^d	serious ⁱ	none detected ^f	4/141 (2.8%)	4/137 (2.9%)	not pooled	not pooled	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The systematic review (Verschueren et al 2018) included studies both with depressed and anxious participants. However, only studies were included in the table here that had people with depression as participants. The included study for this outcome involved exercise 3 days per week for 12 weeks in people with ischemic heart disease and depression; control: weekly group counselling and follow-up with physician; USA.

b. This has been rated as serious, as the authors of the systematic review reported an unclear risk of attrition bias. See Figure 2 in Verschueren et al 2018.

c. Heterogeneity is not relevant/appropriate, as only 1 study was included.

d. This has been rated as serious, as the study included participants with depression rather than SMD overall.

e. This has been rated as very serious, as the total number of participants is very low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.

f. Publication bias was not assessed by the authors of the systematic review (Verschueren et al 2018), so was not detected.

- g. The systematic review (Verschuere et al 2018) included studies both with depressed and anxious participants. However, only studies were included here that had people with depression as participants. The 2 included studies for this outcome were as follows: Exercise 3 days per week for 12 weeks in people with ischemic heart disease and depression; control: weekly group counselling and follow-up with physician; USA. Exercise 2 days per week for 8 weeks plus behavioural counselling and relaxation in people with ischemic heart disease and depression; control: community care; Canada.
- h. This has been rated as serious, since heterogeneity was not assessed in the systematic review (Verschuere et al 2018) due to the variability between studies, but the results of the 2 studies that are included here varied dramatically.
- i. This has been rated as serious, as the 2 included studies both had wide confidence intervals, which both included 'no effect' and appreciable benefit and harm, and the 2 studies produced results in opposing directions (study 1: 0.20 (0.01 to 3.92); study 2: 1.37 (0.32 to 5.98)).

Table 5: Collaborative care vs. care as usual for people with SMD and cardiovascular disease

Author(s): Maya Semrau (first rater), Corrado Barbui (second rater)

Date: April 2018

Question: Collaborative care compared to care as usual for people with SMD and cardiovascular disease

Setting: inpatients and outpatients

Bibliography: Tully J & Baumeister H. Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2015; 5(12): e009128

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	collaborative care	care as usual	Relative (95% CI)	Absolute (95% CI)		
Major adverse cardiovascular event (MACE) - short to medium term (under 12 months) (RR below 1 favours collaborative care)												
3 ^a	randomised trials	very serious ^b	not serious ^c	serious ^d	not serious	none detected ^e	22/303 (7.3%)	42/306 (13.7%)	RR 0.54 (0.31 to 0.95)	63 fewer per 1,000 (from 7 fewer to 95 fewer)	⊕○○○ VERY LOW	CRITICAL
Major adverse cardiovascular event (MACE) - long term (over 12 months) (RR below 1 favours collaborative care)												
1 ^f	randomised trials	very serious ^b	not serious	serious ^d	very serious ^g	none detected ^e	13/80 (16.3%)	12/77 (15.6%)	RR 1.04 (0.51 to 2.14)	6 more per 1,000 (from 76 fewer to 178 more)	⊕○○○ VERY LOW	CRITICAL
Frequency of adverse events / side-effects - mortality (RR below 1 favours collaborative care)												
5 ^h	randomised trials	very serious ^b	not serious ⁱ	serious ^d	serious ^j	none detected ^e	N/A	N/A	RR 1.38 (0.53 to 3.58)	1 fewer per 1,000 (from 1 fewer to 4 fewer)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The 3 included studies were all conducted in the USA and were all single-blind effectiveness RCTs. Two of the studies included participants with either myocardial infarction or unstable angina, and 1 study included participants with coronary artery bypass graft; all participants in the 3 studies had comorbid depression. See Table 1 in Tully & Baumeister 2015.

b. This has been rated as very serious, as all studies had a high risk of bias for masking of outcome assessment. This information was taken from eSupplement 1 in Tully & Baumeister 2015.

c. This has been rated as not serious, as heterogeneity (I²) was reported to be 12% by Tully & Baumeister 2015 (see Figure 2).

d. This has been rated as serious, as the study included participants with depression rather than SMD overall.

- e. The authors of the systematic review (Tully & Baumeister 2015) did not produce funnel plots, as there were less than 10 studies included, but the authors reported no publication bias. See eSupp 15 in Tully & Baumeister 2015.
- f. The included study was conducted in the USA and was a single-blind effectiveness RCT. Participants had either myocardial infarction or unstable angina, with comorbid depression. See Table 1 in Tully & Baumeister 2015.
- g. This has been rated as very serious, as the number of participants is low, and the confidence interval includes both 'no effect' and appreciable harm. This information has been taken from Figure 2 in Tully & Baumeister 2015.
- h. The systematic review (Tully & Baumeister 2015) did not specify which 5 RCTs were included in this analysis.
- i. This has been rated as not serious, though heterogeneity (I²) was not reported for this analysis by Tully & Baumeister 2015 (see page 6).
- j. This has been rated as serious, as the confidence interval includes 'no effect' and appreciable harm.

Cardiovascular risk

Table 6: Metformin vs. placebo for people with SMD and cardiovascular risk factors

Author(s): Maya Semrau

Date: April 2018

Question: Metformin compared to placebo for people with SMD and cardiovascular risk factors

Setting: inpatients and outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

De Silva VA et Al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016; 16(1): 341

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
Adequacy of control of CVD risk factors – blood pressure												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adequacy of control of CVD risk factors - total cholesterol (MD below 0 favours intervention)												
3 ^a	randomised trials	serious ^b	serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	130	125	-	MD 5.38 lower (26.59 lower to 15.82 higher) ^{g,h}	⊕○○○ VERY LOW	CRITICAL
Cardiovascular disease incidence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
5 ⁱ	randomised trials	very serious ^j	not serious ^k	not serious	serious ^l	none detected ^m	The five studies reported on discontinuation (metformin, n=215; placebo, n=211). One of the studies reported discontinuation due to dizziness in metformin group and 3 due to development of diabetes in placebo group; another study reported 11 in the metformin and 8 on placebo discontinued to intolerability; another study reported that 1 in metformin group and 2 in placebo withdrew due to psychosis; a further study reported 3 discontinuations due to nausea and psychosis; the final study reported 5 discontinuations due to psychosis. Only one trial reported diarrhoea was significantly more in the metformin group compared to placebo. Three trials reported no significant difference in moderate adverse events. ⁿ				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- Two of the studies were conducted in Venezuela, and 1 in the USA, with people with schizophrenia or schizoaffective disorder, or bipolar disorder. See Table 1 in Mizuno et al (2014).
- This has been rated as serious, as 2 of the studies had an unclear risk of bias for masking of outcome assessment. This information was taken from Table S1 in Mizuno et al (2014).
- This has been rated as serious, as heterogeneity (I²) was reported to be 57% by Mizuno et al 2014 (see Table S8).
- This has been rated as serious, as having high blood pressure or cholesterol were not inclusion criteria.
- This has been rated as serious, as the confidence intervals include both 'no effect' and appreciable benefit and harm.
- Funnel plots produced by the authors of the systematic review (Mizuno et al 2014) showed the possibility of publication bias (see Figure S9).
- This information was taken from Table S8 in Mizuno et al (2014).
- There were also no significant effects on LDL-cholesterol (-4.43, -34.23, 25.36) or HDL-cholesterol (0.33, -2.80, 3.46). See Tables S9 and S10 in Mizuno et al 2014.
- The 5 studies were conducted in China (n=3), Sri Lanka (n=1), and the USA (n=1). All studies included participants who had schizophrenia or schizoaffective disorder, and who were taking anti-psychotics. Three of the studies also included diet/nutrition and/or exercise counselling (in both the intervention and placebo group). The interventions ranged between 12 and 24 weeks. See Table 1 in de Silva et al (2016).
- This has been rated as very serious, as 3 of the studies had an unclear risk for blinding. This information was taken from supplementary Table 1 in de Silva et al (2016).
- This has been rated as not serious, as data were not pooled, and so heterogeneity could not be established.

- l. This has been rated as serious, as data were not pooled, effect sizes are not clear, and results do not appear consistent across studies.
- m. Funnel plots were produced by the authors of the systematic review (de Silva et al 2016), which detected no publication bias. See Figure 8 in de Silva et al (2016).
- n. This information was taken from page 4 in de Silva et al (2016).

Table 7: Aripiprazole vs. placebo for people with SMD and cardiovascular risk factors

Author(s): Maya Semrau

Date: April 2018

Question: Aripiprazole compared to placebo for people with SMD and cardiovascular risk factors

Setting: inpatients and outpatients

Bibliography:

Mizuno Y et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull. 2014; 40(6): 1385-1403

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	aripiprazole	placebo	Relative (95% CI)	Absolute (95% CI)		
Adequacy of control of CVD risk factors – blood pressure												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adequacy of control of CVD risk factors - total cholesterol (MD below 0 favours intervention)												
3 ^a	randomised trials	very serious ^b	not serious ^c	serious ^d	not serious	none detected ^e	128	117	-	MD 12.81 lower (19.35 lower to 6.27 lower) ^f	⊕○○○ VERY LOW	CRITICAL
Cardiovascular disease incidence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects												
1 ^g	randomised trials	very serious ^h	not serious	not serious	serious ⁱ	none detected ^j	One participant in the placebo arm and five in the aripiprazole arm discontinued the trial due to adverse effects. 0 out of 99 patients in the placebo group and 10 out of 108 patients in the aripiprazole group experienced a serious adverse effect. ^k				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. Two of the studies were conducted in the USA, and 1 in Austria, with participants who had either schizophrenia or schizoaffective disorders, and were taking either clozapine or olanzapine. The studies ranged between 8 and 16 weeks. See Table 1 in Mizuno et al (2014).
- b. This has been rated as very serious, as all 3 studies had an unclear risk for masking of outcome assessment, and 1 study had uneven drop-out rates. This information was taken from Table S1 in Mizuno et al (2014).
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% in Mizuno et al 2014 (see Table S8).
- d. This has been rated as serious, as having high blood pressure or cholesterol were not inclusion criteria.
- e. A funnel plot was produced by the authors of the systematic review (Mizuno et al 2014), and no publication bias was detected. See Figure S9 in Mizuno et al (2014).
- f. This information was taken from Table S8 in Mizuno et al (2014).

- g. Gierisch et al (2013, 2014) reported adverse events for aripiprazole in their systematic review. They identified 1 study, which was conducted in Austria, with participants who had schizophrenia and were taking clozapine, and had experienced weight gain.
- h. This has been rated as very serious, as the study had an unclear risk for masking of outcome assessment.
- i. This has been rated as serious, as results come from one study and were not pooled.
- j. Funnel plots were not produced by the authors of the systematic review (Gierisch et al 2013).
- k. This information has been taken from page 27 in Gierisch et al (2013).

Table 8: Lifestyle interventions compared to care as usual for people with SMD and cardiovascular risk factors

Author(s): Maya Semrau

Date: April 2018

Question: Lifestyle interventions compared to care as usual for people with SMD and cardiovascular risk factors

Setting: inpatients and outpatients

Bibliography:

Teasdale SB et al. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017; 210(2): 110-18

Gierisch et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Reviews: 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	lifestyle interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
Adequacy of control of CVD risk factors - systolic blood pressure (MD below 0 favours intervention)												
7 ^a	randomised trials	very serious ^b	serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	^g	^g	-	MD 0.63 higher (1.86 lower to 3.12 higher) ^h	⊕○○○ VERY LOW	CRITICAL
Adequacy of control of CVD risk factors - diastolic blood pressure (MD below 0 favours intervention)												
6 ^a	randomised trials	very serious ^b	serious ⁱ	serious ^d	serious ^e	publication bias strongly suspected ^f	^g	^g	-	MD 1.69 lower (3.6 lower to 0.23 higher) ^h	⊕○○○ VERY LOW	CRITICAL
Adequacy of control of CVD risk factors - total cholesterol (MD below 0 favours intervention)												
7 ^j	randomised trials	very serious ^k	not serious ^l	serious ^d	not serious	publication bias strongly suspected ^f	^g	^g	-	MD 0.13 lower (0.29 lower to 0.03 higher) ^h	⊕○○○ VERY LOW	CRITICAL
Cardiovascular disease incidence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	lifestyle interventions	care as usual	Relative (95% CI)	Absolute (95% CI)		
Frequency of adverse events/side-effects												
1 ^m	randomised trials	very serious ⁿ	not serious	serious ^d	very serious ^o	none detected ^p	N=33. No severe adverse effects were observed. ^q				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. The studies were conducted with participants who had SMD (e.g. schizophrenia spectrum disorder, bipolar affective disorder, depression with psychotic features). The interventions included nutritional interventions. It was not clear from the systematic review (Teasdale et al 2017) exactly which of a possible 8 studies were included in this analysis (this was a secondary analysis). See Tables 1 and DS1 in Teasdale et al 2017.
- b. This has been rated as very serious, as even though it is not clear exactly which studies were included, half of the possible 8 studies did not have masking of outcome assessment. This information was taken from Table DS2 in Teasdale et al 2017.
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 54% by Teasdale et al 2017 (see Table 1).
- d. This has been rated as serious, as having high blood pressure or cholesterol levels were not specific inclusion criteria in the systematic review (Teasdale et al 2017).
- e. This has been rated as serious, as the confidence intervals include both 'no effect' and appreciable benefit and harm.
- f. The authors of the systematic review (Teasdale et al 2017) did find some evidence of publication bias, though after recalculating the effect sizes using Duval & Tweedie's trim and fill method their results were broadly similar. See page 116 in Teasdale et al (2017).
- g. The exact participant numbers were not clear from the systematic review (Teasdale et al 2017), but total numbers were over 200 in any case.
- h. This information was taken from Table 1 in Teasdale et al (2017).
- i. This has been rated as serious, as heterogeneity (I²) was reported to be 61% by Teasdale et al 2017 (see Table 1).
- j. The 7 studies were conducted with participants who had SMD (e.g. schizophrenia spectrum disorder, bipolar affective disorder, depression with psychotic features). The interventions included nutritional interventions. It was not clear from the systematic review exactly which of a possible 10 studies were included in this analysis (this was a secondary analysis). See Tables 1 and DS1 in Teasdale et al 2017.
- k. This has been rated as very serious, as 8 of the 10 possible studies did not have masking of outcome assessment. See Table DS2 in Teasdale et al (2017).
- l. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Teasdale et al 2017 (see Table 1).
- m. Gierisch et al (2013, 2014) identified 1 relevant study that assessed adverse effects. The study was conducted in Italy, and involved psychoeducation with individualised diet and food diary, for participants who had schizophrenia, bipolar disorder or psychotic depression.
- n. This has been rated as serious, as the study did not have masking of outcome assessment. This information was taken from Gierisch et al 2013.
- o. This has been rated as very serious, as the number of participants was very low.
- p. Publication bias was not assessed by the authors of the systematic review (Gierisch et al 2013) due to the small number of studies.
- q. This information was taken from page 42 in Gierisch et al 2013.

Additional evidence not mentioned in GRADE tables³

Agarwal et al (2017) conducted a Cochrane meta-analysis (published as conference proceedings so far) to determine the effects of pharmacological interventions aimed at reduction or prevention of weight gain in schizophrenia. Forty-four randomized controlled trials met the inclusion criteria for this review. Metformin (weight: n = 106, 3 RCTs, MD -3.40 kg CI -6.71 to -0.08; BMI: n = 106, 3 RCTs, MD= -1.29, CI = -2.29 to -0.29), reboxetine (weight: n = 79, 2 RCTs MD= -1.90, CI = -3.07 to -0.72; BMI: n= 79, 2 RCTs, MD= -0.68, CI= -1.08 to -0.28), and reboxetine-betahistine (weight: n= 32, 1 RCT MD= -2.75, CI = -4.94 to -0.56; BMI: n= 32, 1 RCT, MD= -0.74, CI= -1.35 to -0.13) were found to have a modest effect in preventing weight gain and change in BMI while topiramate (n= 67, 1 RCT, MD -2.45 kg/m² CI -4.39 to -0.51 kg/m²) prevented a change in body mass index (BMI) in patients started on antipsychotic treatment. In terms of treatments for weight loss, we found significantly greater reduction in weight in patients treated with metformin (n= 541, 7 RCTs, MD -3.42 kg CI -4.96 to -1.88 kg), aripiprazole (n = 236, 2 RCTs, MD -2.00 kg CI -2.96 to -1.03 kg), nizatidine (n =113, 3 RCTs, MD -4.42 kg CI -8.10 to -0.73 kg), sibutramine (n= 68, 4 RCTs, MD -5.42 kg CI -8.33 to -2.51 kg), and topiramate (200 mg but not 100 mg) (n =37, 1 RCT, MD -5.05 kg CI -7.67 to -2.43 kg), and significantly greater reduction in BMI in patients treated with metformin (n= 578, 8 RCTs, MD -1.31 kg/m² CI -1.85 to -0.78 kg/ m²), sibutramine (n= 68, 4 RCTs, MD -1.09 kg/m² CI -1.88 to -0.30 kg/m²), and topiramate (200 mg but not 100 mg) (n= 37, 1 RCT, MD -1.91 kg/m² CI -3.11 to -0.71 kg/m²) compared with placebo. Importantly, none of the adjunctive treatment strategies resulted in worsening of mental status or in higher dropout rates; topiramate may in fact be associated with improvement in clinical status while reboxetine and reboxetine-betahistine might decrease depressive symptoms. Among the agents that led to a significant decrease in weight, metformin, topiramate, nizatidine, reboxetine, reboxetinebetahistine, and sibutramine did not differ compared to placebo with respect to the frequency of adverse effects, while aripiprazole resulted in significantly higher occurrence of nausea and anxiety. Authors' conclusions: Accumulating evidence supports the safe use of pharmacological interventions to achieve modest weight loss. Metformin has the most evidence for use both for prevention as well as treatment of weight gain in schizophrenia. Other agents showing positive effects include aripiprazole, topiramate, nizatidine, reboxetine, reboxetine-betahistine, and sibutramine. However, interpretation for these agents is limited by the small number of studies, small sample size, and short study duration. Future studies adequately powered, with longer treatment duration will be needed in further evaluating the efficacy and safety of interventions for managing weight gain.

Liu et al (2015) conducted a systematic review about the use of metformin to treat clozapine-induced weight gain in adults with schizophrenia. Six studies with a pooled sample of 207 treatment-group patients and 207 control-group patients were included – three double-blind, placebo-controlled RCTs and three RCTs that did not use placebo controls and were not blinded. The meta-analysis found that compared to the control condition, patients receiving metformin experienced significantly greater reductions in body weight (mean difference [MD] = -2.89 kg, 95% CI: -4.20 to -1.59 kg) and body mass index (BMI) (MD = -0.81, 95% CI: -1.16 to -0.45), but there was no significant difference between the groups in the prevalence of side effects. Authors' conclusions: Adjunctive treatment with metformin appears to be effective for treating clozapine-induced weight gain and elevations in BMI in adult patients with schizophrenia. However, the quality of the evidence about the safety of this treatment is low, follow-up time in the available studies is relatively short, and half of the studies did not employ blinded assessment of outcome measures. Larger studies with placebo controls that follow

³ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

patients for at least 24 weeks and that make blinded assessments of a range of relevant outcome measures (weight, BMI, blood lipids, insulin resistance, etc.) are needed to confirm these results.

Richards et al (2017): *Background:* Coronary heart disease (CHD) is the most common cause of death globally, although mortality rates are falling. Psychological symptoms are prevalent for people with CHD, and many psychological treatments are offered following cardiac events or procedures with the aim of improving health and outcomes. This is an update of a Cochrane systematic review previously published in 2011. *Objectives:* To assess the effectiveness of psychological interventions (alone or with cardiac rehabilitation) compared with usual care (including cardiac rehabilitation where available) for people with CHD on total mortality and cardiac mortality; cardiac morbidity; and participant reported psychological outcomes of levels of depression, anxiety, and stress; and to explore potential study-level predictors of the effectiveness of psychological interventions in this population. *Search methods:* We updated the previous Cochrane Review searches by searching the following databases on 27 April 2016: CENTRAL in the Cochrane Library, MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), and CINAHL (EBSCO). *Selection criteria:* We included randomised controlled trials (RCTs) of psychological interventions compared to usual care, administered by trained staff, and delivered to adults with a specific diagnosis of CHD. We selected only studies estimating the independent effect of the psychological component, and with a minimum follow-up of six months. The study population comprised of adults after: a myocardial infarction (MI), a revascularisation procedure (coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)), and adults with angina or angiographically defined coronary artery disease (CAD). RCTs had to report at least one of the following outcomes: mortality (total- or cardiac-related); cardiac morbidity (MI, revascularisation procedures); or participant-reported levels of depression, anxiety, or stress. *Data collection and analysis:* Two review authors independently screened titles and abstracts of all references for eligibility. A lead review author extracted study data, which a second review author checked. We contacted study authors to obtain missing information. *Main results:* This review included 35 studies which randomised 10,703 people with CHD (14 trials and 2577 participants added to this update). The population included mainly men (median 77.0%) and people post-MI (mean 65.7%) or after undergoing a revascularisation procedure (mean 27.4%). The mean age of participants within trials ranged from 53 to 67 years. Overall trial reporting was poor, with around a half omitting descriptions of randomisation sequence generation, allocation concealment procedures, or the blinding of outcome assessments. The length of follow-up ranged from six months to 10.7 years (median 12 months). Most studies (23/35) evaluated multifactorial interventions, which included therapies with multiple therapeutic components. Ten studies examined psychological interventions targeted at people with a confirmed psychopathology at baseline and two trials recruited people with a psychopathology or another selecting criterion (or both). Of the remaining 23 trials, nine studies recruited unselected participants from cardiac populations reporting some level of psychopathology (3.8% to 53% with depressive symptoms, 32% to 53% with anxiety), 10

studies did not report these characteristics, and only three studies excluded people with psychopathology. Moderate quality evidence showed no risk reduction for total mortality (risk ratio (RR) 0.90, 95% confidence interval (CI) 0.77 to 1.05; participants = 7776; studies = 23) or revascularisation procedures (RR 0.94, 95% CI 0.81 to 1.11) with psychological therapies compared to usual care. Low quality evidence found no risk reduction for non-fatal MI (RR 0.82, 95% CI 0.64 to 1.05), although there was a 21% reduction in cardiac mortality (RR 0.79, 95% CI 0.63 to 0.98). There was also low or very low quality evidence that psychological interventions improved participant-reported levels of depressive symptoms (standardised mean difference (SMD) -0.27, 95% CI -0.39 to -0.15; GRADE = low), anxiety (SMD -0.24, 95% CI -0.38 to -0.09; GRADE = low), and stress (SMD -0.56, 95% CI -0.88 to -0.24; GRADE = very low). There was substantial statistical heterogeneity for all psychological outcomes but not clinical outcomes, and there was evidence of small-study bias for one clinical outcome (cardiac mortality: Egger test $P = 0.04$) and one psychological outcome (anxiety: Egger test $P = 0.012$). Meta-regression exploring a limited number of intervention characteristics found no significant predictors of intervention effects for total mortality and cardiac mortality. For depression, psychological interventions combined with adjunct pharmacology (where deemed appropriate) for an underlying psychological disorder appeared to be more effective than interventions that did not ($\beta = -0.51$, $P = 0.003$). For anxiety,

interventions recruiting participants with an underlying psychological disorder appeared more effective than those delivered to unselected populations ($\Delta = -0.28$, $P = 0.03$). *Authors' conclusions:* This updated Cochrane Review found that for people with CHD, there was no evidence that psychological treatments had an effect on total mortality, the risk of revascularisation procedures, or on the rate of non-fatal MI, although the rate of cardiac mortality was reduced and psychological symptoms (depression, anxiety, or stress) were alleviated; however, the GRADE assessments suggest considerable uncertainty surrounding these effects. Considerable uncertainty also remains regarding the people who would benefit most from treatment (i.e. people with or without psychological disorders at baseline) and the specific components of successful interventions. Future large-scale trials testing the effectiveness of psychological therapies are required due to the uncertainty within the evidence. Future trials would benefit from testing the impact of specific (rather than multifactorial) psychological interventions for participants with CHD, and testing the targeting of interventions on different populations (i.e. people with CHD, with or without psychopathologies).

Zimbron et al (2016): Metabolic complications are commonly found in people treated with clozapine. Reviews on the management of this problem have generally drawn conclusions by grouping different types of studies involving patients treated with various different antipsychotics. We carried out a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity or metabolic syndrome. Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine. We identified 15 RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil, and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations treated with different antipsychotics. We conclude that randomised-controlled trial data support the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine.

Lally J et al (2016) conducted a Cochrane review, to assess the clinical effects and efficacy of pharmacological interventions for clozapine-induced sinus tachycardia. Searches were performed on 23 March 2015. No randomised controlled trials were identified that met the inclusion criteria. *Authors' conclusions:* With no studies meeting the inclusion criteria, it is not possible to arrive at definitive conclusions. There are currently insufficient data to confidently inform clinical practice. We cannot, therefore, conclude whether specific interventions, such as beta-blockers, are less effective or more effective than standard courses of alternative treatments for tachycardia. One trial is currently underway.

Bisogni V et al (2015) conducted a systematic review assessing antihypertensive therapy in patients affected by bipolar disorders (BD) treated with lithium. The authors found that signs and symptoms of overt Lithium intoxication occurred with agents that reduce the renal clearance of lithium. They were resolved mostly with withdrawal of the offending antihypertensive drug and forced alkaline diuresis, and with haemodialysis in the most severe cases. Severity of symptoms of Lithium toxicity showed a direct correlation ($p < 0.05$) with total daily dose of Lithium. However, at regression analysis Lithium toxicity was not predicted by age, baseline serum Li and creatinine levels, nor by any class of antihypertensive drugs. *Authors conclusions:* Given the unfeasibility of predicting Lithium toxicity, strict monitoring of patient's clinical conditions and Lithium levels is key for early detection of this potentially fatal conditions in hypertensive patients with BD treated with Lithium and antihypertensive drugs.

Jeyanantham et al (2017) conducted a meta-analysis to evaluate the effects of cognitive behavioural therapy (CBT) on depression, quality of life, hospitalisations and mortality in heart failure patients. Six studies were identified: 5 RCTs and 1 observational study, comprising 320 participants with predominantly NYHA classes II-III, who were mostly male, with mean age ranging from 55 to 66 years. Compared to usual care, CBT was associated with a greater improvement in depression scores both initially after CBT sessions (standardised mean difference -0.34, 95% CI -0.60 to -0.08, $p = 0.01$) and at 3 months follow-up (standardised mean difference -0.32, 95% CI -0.59 to -0.04, $p = 0.03$). Greater improvement in quality of life scores was evident for the CBT group initially after CBT sessions, but with no difference at 3 months. Hospital admissions and mortality were similar, regardless of treatment group. The authors concluded that CBT may be more effective than usual care at improving depression scores and quality of life for heart failure patients initially following CBT and for depression at 3 months. Larger and more robust RCTs are needed to evaluate the long-term clinical effects of CBT in heart failure patients.

Rajeswaran et al (2017) conducted a systematic review aimed to compile studies examining whether the use of antidepressants could improve outcomes in patients with heart failure (HF) and concomitant depression. Five studies met the inclusion criteria. Three of these papers were randomised controlled trials (RCT); the other two, cohort studies. All studies show that antidepressants are well tolerated in this group. There was no significant difference in depressive symptoms between the test and placebo. The cardiac outcomes of patients with HF were not improved by the use of antidepressants relative to placebo. Authors conclusions: Antidepressants are not associated with increased mortality rate as established in previous papers. However, there is inadequate evidence that the use of antidepressants effects significant improvement in depression or cardiac outcomes. Please note that this systematic review was graded as of low quality according to AMSTAR.

Ramamurthy et al (2013) conducted a systematic review of randomized controlled trials reporting on the medical outcomes of depression treatment among patients with established coronary artery disease. The review yielded 10 trials. Antidepressant and/or psychotherapy did not significantly influence coronary artery disease outcomes in the overall population, but most studies were underpowered. There was a trend toward worse coronary artery disease outcomes after treatment with bupropion. Authors conclusions: After an acute coronary syndrome, depression often spontaneously remitted without treatment. Post-acute coronary syndrome persistence of depression predicted adverse coronary artery disease outcomes. Antidepressant and/or psychotherapy, particularly as part of the Coronary Psychosocial Evaluation Studies intervention, may improve prognosis in persistent depression among post-acute coronary syndrome patients. Noradrenergic antidepressants should be prescribed cautiously in patients with coronary artery disease.

Reid et al (2013) & Thompson et al (2013) conducted a systematic review to assess evidence on the effectiveness of psychological interventions for patients with coronary heart disease (CHD) and their partners. Results: Seven RCTs comprising 673 dyads (patient and partner) were included. Psychological interventions resulted in modest improvements in patients' health-related quality of life, blood pressure, knowledge of disease and treatment, and satisfaction with care, and in partners' anxiety, knowledge and satisfaction. There was a non-significant trend for improvements in anxiety for patients, and depressive symptoms for both patients and partners. There was no evidence of a significant effect on mortality, morbidity or other cardiovascular risk factors for patients, or social support for patients and partners. Authors' conclusions: Psychological interventions for patients with CHD and their partners were found to improve health-related quality of life, blood pressure, knowledge, and satisfaction with care for patients, and anxiety, knowledge, and satisfaction with care for partners. However, the small number of studies included in the review had generally poor methodology, as shown by the risk of bias, and were performed over 10 years ago. As only two of the seven studies resulted in modest improvements in outcomes, no firm conclusions can be drawn as to the effectiveness of such interventions in this population.

Rustad et al (2013) sought to review the prevalence, diagnosis, neurobiology, and treatment of depression associated with congestive heart failure. Results: MDD is highly prevalent in patients with congestive heart failure. Moreover, the prevalence and severity of depression correlates with the degree of cardiac dysfunction and development of congestive heart failure. Depression increases the risk of congestive heart failure, particularly in those patients with coronary artery disease, and is associated with a poorer quality of life, increased use of health care resources, more frequent adverse clinical events and hospitalizations, and twice the risk of mortality. Authors conclusions: At present, limited empirical data exist with regard to treatment of depression in the increasingly large population of patients with congestive heart failure. Evidence reveals that both psychotherapeutic treatment (e.g. cognitive-behavioral therapy) and pharmacologic treatment (e.g. use of the selective serotonin reuptake inhibitor sertraline) are safe and effective in reducing depression severity in patients with cardiovascular disease. Collaborative care programs featuring interventions that work to improve adherence to medical and psychiatric treatments improve both cardiovascular disease and depression outcomes.

Rutledge et al (2013) conducted a meta-analysis, to quantify the efficacy of mental health (antidepressants & psychotherapies) and cardiac rehabilitation treatments for improving secondary event risk and depression among patients with coronary heart disease (CHD). Results: Eighteen mental health trials evaluated secondary events and 22 trials evaluated depression reduction. Cardiac rehabilitation trials for the same categories numbered 17 and 13, respectively. Mental health treatments did not reduce total mortality (absolute risk reduction [ARR] = -0.001, confidence interval [95% CI] = -0.016 to 0.015; number needed to treat [NNT] = ∞), showed moderate efficacy for reducing CHD events (ARR = 0.029, 95% CI = 0.007 to 0.051; NNT = 34), and a medium effect size for improving depression (Cohen d = 0.297). Cardiac rehabilitation showed similar efficacy for treating depression (d = 0.23) and reducing CHD events (ARR = 0.017, 95% CI = 0.007 to 0.026; NNT = 59) and reduced total mortality (ARR = 0.016, 95% CI = 0.005 to 0.027; NNT = 63). Authors' conclusions: Among patients with CHD, mental health treatments and cardiac rehabilitation may each reduce depression and CHD events, whereas cardiac rehabilitation is superior for reducing total mortality risk. The results support a continued role for mental health treatments and a larger role for mental health professionals in cardiac rehabilitation.

Relevant guidelines

The NICE guidelines *Psychosis and schizophrenia in adults: prevention and management* (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014) includes the following relevant recommendations:

- Medication choice should involve information and discussing benefits and side effects, considering metabolic side effects (including weight gain and diabetes)
- GPs and primary health care professionals should monitor physical health of people with psychosis (when transferred to primary care from secondary care, and then at least annually); comprehensive health checks and refer to relevant NICE guidance on monitoring cardiovascular disease, diabetes, obesity and respiratory disease.
- "Physical health" recommendations: routinely monitored/audit weight, and cardiovascular and metabolic indicators of morbidity; should be audited in annual team report. Performance indicators should be used to ensure compliance with quality standards on monitoring and treating cardiovascular and metabolic disease.
- Before starting medication should offer person ECG if "physical examination has identified specific cardiovascular risk, or if there is personal history of cardiovascular disease"

- Should identify people who have CVD, high blood pressure, abnormal lipid levels, are obese/at risk of obesity, have diabetes/at risk of diabetes (as indicated by abnormal blood glucose levels), or physically inactive, at the earliest opportunity following relevant NICE guidance for these conditions.
- For hypertension, recommends identifying people with high blood pressure, and following relevant NICE guidance (Hypertension CG 127); should identify people who have high blood pressure, abnormal lipid levels, are obese/at risk of obesity, have diabetes/at risk of diabetes (as indicated by abnormal blood glucose levels), or physically inactive, at the earliest opportunity following relevant NICE guidance for these conditions.
- Since 2015 NICE also endorse the "Lester UK adaptation of the Australian Positive Cardiometabolic Health Resource" as related to the Psychosis NICE guideline ("a clinical tool that summarizes safe interventions to help frontline staff make assessments of cardiac and metabolic health in persons with SMD"). In "monitoring physical care" recommends identifying people with high blood pressure, and following relevant NICE guidance (Public Health guideline PH25 on Cardiovascular Disease Prevention; 2010).

The NICE guidelines *Bipolar disorder: assessment and management* (Clinical guideline [CG185]; Published date: September 2014 Last updated: February 2016) include the following relevant recommendations:

- Included in health check: weight or BMI, diet, nutritional status and level of physical activity cardiovascular status, including pulse and blood pressure metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile
- Before starting antipsychotic medication, should measure and record: weight or BMI, pulse, blood pressure, fasting blood glucose or HbA1c blood lipid profile.
- Before starting antipsychotic medication should offer person ECG if "physical examination has identified specific cardiovascular risk (hypertension, cardiac arrhythmia), or if there is personal history of cardiovascular disease"
- Regarding use of Lithium: need to take into account risk factors for cardiovascular disease.

The NICE guidelines *Depression in adults with a chronic physical health problem: recognition and management* (Clinical guideline [CG91]; Published date: October 2009) include the following relevant recommendations:

- When prescribing lithium, EEG monitoring recommended for people with depression at high risk of cardiovascular disease.
- When prescribing an antipsychotic, monitor weight, lipid and glucose levels, and side effects.
- When prescribing drugs other than SSRIs, take into account cautions, contraindications and monitoring requirements. E.g. potential for higher doses of venlafaxine to exacerbate cardiac arrhythmias, and the need to monitor the person's blood pressure, the possible exacerbation of hypertension with venlafaxine and duloxetine.

Cooper et al (2016)'s *BAP guidelines* recommend the following in cardiovascular risk management for people with psychosis:

- The measurements below should be assessed before starting an antipsychotic, or as soon as possible afterwards, and then at the intervals indicated.

- Body mass index (BMI) should be used to monitor whether an individual is becoming overweight or obese. This requires frequent measurement of weight during the early stages of treatment: ideally weekly for the first 4–6 weeks and then every 2–4 weeks up to 12 weeks; but, as a minimum, once every 4 weeks for the first 12 weeks' of treatment. Weight (and BMI) should then be assessed at 6 months and at least annually thereafter, unless the clinical situation demands more frequent assessment. It is important to take ethnicity into account when evaluating BMI results.
- The lipid profile should be assessed at 12 weeks, 6 months and then annually. In order to assess cardiovascular risk, for example using the QRISK2 cardiovascular risk model, the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio will be required. A random, rather than fasting, sample can be used if a fasting sample cannot be obtained.
- Blood pressure should be monitored at 12 weeks, 6 months and annually thereafter.
- If there is a change in antipsychotic medication then, when clinically relevant, it is appropriate to re-visit all of the steps outlined above. The management of the medical consequences of weight gain and obesity should be in primary care. Initial investigations may be by either the mental health team or the primary care team.
- The prescription of metformin for those not responding to intensive lifestyle interventions needs to be considered in the context of the individual.
- Hypertension should be managed according to standard NICE guidelines. Practitioners should be aware of possible increased hypotensive effects when some antihypertensive medications are combined with antipsychotics.

Also see Taylor et al, *The Maudsley Prescribing Guidelines in Psychiatry* (new edition published in May 2018).

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Beta-blockers have significant interactions with multiple psychiatric medications. *For bisoprolol, metoprolol, and carvedilol:* Advise caution and monitor therapy with **risperidone, chlorpromazine, fluphenazine, and clozapine** due to elevated risk for hypotension. Additionally, **chlorpromazine** and **fluphenazine** can increase the levels of these beta-blockers (and vice versa), which increases the risk of toxicity of both the antipsychotic and the beta-blocker. *For atenolol,* advise caution and monitor therapy with **risperidone, chlorpromazine, and clozapine** due to elevated risk for hypotension. *For metoprolol and carvedilol only:* consider alternative to concomitant use with **fluoxetine**, as fluoxetine may elevate levels of these beta-blockers. If used concurrently, monitor for signs of beta-blocker toxicity including hypotension, bradycardia, and heart block/prolonged PR interval. *For bisoprolol only:* consider alternative to concomitant use of bisoprolol and **carbamazepine**, as carbamazepine may reduce the levels (and efficacy) of bisoprolol.

Anti-anginal medication. *Glyceryl trinitrate:* Monitor therapy with **amitriptyline, haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, biperiden, and trihexyphenidyl**, as medications with anticholinergic effects can cause xerostomia (dry mouth), which can affect absorption of sublingual formulations of glyceryl trinitrate. If xerostomia develops, patients should be advised to utilize strategies to counteract this including

artificial saliva and chewing gum. *Isosorbide dinitrate*: Advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Consider alternative to concomitant use of isosorbide dinitrate and **carbamazepine**. Carbamazepine may reduce the levels (and efficacy) of isosorbide dinitrate.

Verapamil: *With regards to antipsychotics*: Monitor therapy with **haloperidol**, **risperidone**, and **clozapine**, as verapamil may elevate the levels of these medicines. Advise caution and monitor therapy with **chlorpromazine** due to elevated risk for hypotension. *With regards to mood stabilizing medication*: Verapamil may affect levels of **lithium** and increase the neurotoxicity associated with lithium. The latter effect may not be reflected by elevated drug levels. Monitor clinically for neurotoxicity, as well as lithium levels via laboratory testing when titrating verapamil. Consider alternative to concomitant use of verapamil and **carbamazepine**. Carbamazepine may reduce the levels (and efficacy) of verapamil, and verapamil may elevate the levels of carbamazepine. Verapamil may also increase the levels of **diazepam**.

Amiodarone: Amiodarone is considered to be a high-risk medication with regards to QT interval prolongation. Avoid using amiodarone with other medications that may increase this effect (and the risk of ventricular arrhythmias including torsades de pointes), including amitriptyline, fluoxetine, haloperidol, risperidone, chlorpromazine, clozapine, and lithium. **Fluoxetine** is considered to be high-risk for QT interval prolongation. **Haloperidol**, **risperidone**, **chlorpromazine**, and **clozapine** carry moderate risk for QT-prolongation. **Amitriptyline** and **lithium** carry indeterminate risk for QT-prolongation and may be risk-modifiers; if amitriptyline or lithium is used, monitor for QT-prolongation and arrhythmias by ECG. Consider alternative to concomitant use of amiodarone and **carbamazepine**, as carbamazepine may reduce the levels (and efficacy) of amiodarone.

Amlodipine: Advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Consider alternative to concomitant use of amlodipine and **carbamazepine**. Carbamazepine may reduce the levels (and efficacy) of amlodipine.

Enalapril: Advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Enalapril can increase lithium levels, and the onset of this effect may be delayed. If used concomitantly, consider decreasing the lithium dosing when enalapril is started.

Losartan: Advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Losartan can increase **lithium** levels, and the onset of this effect may be delayed for weeks. If used concomitantly, consider decreasing the dose of lithium when losartan is started or up-titrated. Monitor for signs of lithium toxicity both clinically and via laboratory testing. Consider alternative to concomitant use of losartan and **carbamazepine**, as carbamazepine may reduce the levels (and efficacy) of losartan.

Diuretics. *Hydrochlorothiazide*: Levels of HCTZ may be increased by anticholinergic medication such as **amitriptyline**, **haloperidol**, **risperidone**, **chlorpromazine**, **fluphenazine**, **clozapine**, **biperiden**, and **trihexyphenidyl** due to their effects in decreasing gut motility. Monitor for side effects of HCTZ. Additionally, advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Concomitant use of HCTZ and **fluoxetine** or **carbamazepine** may increase the risk of hyponatremia. Monitor patients for clinical signs of hyponatremia including headache, dizziness, nausea, confusion, and seizures. HCTZ can increase **Lithium** levels. If used concomitantly, consider decreasing the lithium dosing by half when HCTZ is started. Monitor for signs of lithium toxicity both clinically and via laboratory testing. *Furosemide*: Consider alternative to concomitant use of furosemide and **risperidone**, as this combination was linked to increased mortality in patients with dementia. If used concomitantly, patients should be monitored, especially with regards to hydration status. Advise caution and monitor therapy with **chlorpromazine** and **clozapine** due to elevated risk for hypotension. Furosemide may affect levels of **lithium**; this effect is unclear, as it may either increase or reduce

levels. Monitor lithium levels via laboratory testing and for clinical efficacy when titrating furosemide. *Spironolactone*: Advise caution and monitor therapy with **risperidone**, **chlorpromazine**, and **clozapine** due to elevated risk for hypotension. Spironolactone may or may not increase levels of **lithium**; this effect is unclear and the severity of this interaction is considered to be minor.

Aspirin: **Amitriptyline** and **fluoxetine** may increase the risk of bleeding, especially gastrointestinal bleeding, for patients on aspirin. Monitor for signs of bleeding. Aspirin may elevate levels of **valproic acid**. Monitor for toxicity of valproic acid when aspirin is started or up-titrated; conversely, monitor for reduced efficacy of valproic acid when aspirin is down-titrated or stopped.

Clopidogrel: Consider alternative to concomitant use of clopidogrel and **fluoxetine**. Fluoxetine may reduce levels of the active metabolite of clopidogrel. If used concurrently, monitor for reduced efficacy of clopidogrel.

Simvastatin: Concomitant use of simvastatin and **risperidone** may increase the risk of myopathy and rhabdomyolysis. Patients on both medications should be monitored clinically for any symptoms concerning for these conditions. Consider alternative to concomitant use of simvastatin and **carbamazepine**, as carbamazepine may reduce the levels (and efficacy) of simvastatin

Metformin: **Fluoxetine** may increase the potency of hypoglycemics such as metformin. Monitor blood glucose control and adjust dosing of hypoglycemics accordingly, especially when starting or stopping fluoxetine. **Risperidone** and **clozapine** are associated with hyperglycemia and as such, may decrease the efficacy of hypoglycemic medication including metformin. Monitor glycemic control and adjust dosing of hypoglycemic medications accordingly.

There are no significant interactions between **Digoxin** and medicines used for SMD.

See Annex for further information.

WHO guidelines for general population

The WHO guidelines *Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings* (2010) include the following relevant recommendations for the general population:

- Primary prevention of heart attacks and strokes:
 - Tobacco cessation, Regular physical activity 30 minutes a day, Reduced intake of salt <5 g per day, Fruits and vegetables at least 400g per day
 - Aspirin, statins and antihypertensives for people with 10-year cardiovascular risk >30%
 - Antihypertensives for people with blood pressure $\geq 160/100$
 - Antihypertensives for people with persistent blood pressure $\geq 140/90$ and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures
- Acute myocardial infarction: Aspirin
- Secondary prevention (post myocardial infarction):
 - Tobacco cessation, healthy diet and regular physical activity
 - Aspirin, angiotensin-converting enzyme inhibitor, beta-blocker, statin
- Secondary prevention (post stroke):
 - Tobacco cessation, healthy diet and regular physical activity.
 - Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin
- Secondary prevention (Rheumatic heart disease):
 - Regular administration of antibiotics to prevent streptococcal pharyngitis and recurrent acute rheumatic fever

Summary of findings tables

Cardiovascular disease

	Outcome	RR/OR/HR <i>values below 1 favour intervention</i>
GRADE Table 1 (Maslej et al 2017) Antidepressants vs. care as usual (1)	Major adverse cardiovascular event (MACE)	HR 0.93 (0.82 to 1.06) VERY LOW
	Frequency of adverse events/side-effects	HR 0.90 (0.76 to 1.07) VERY LOW
GRADE Table 2 (Nieuwsma et al 2017) Antidepressants vs. care as usual (2)	Major adverse cardiovascular event (MACE)	OR 1.07 (0.57 to 2.00) VERY LOW
	Frequency of adverse events/side-effects	NR
GRADE Table 3 (Ski et al 2016) Psychosocial interventions vs. care as usual	Major adverse cardiovascular event (MACE) - cardiovascular mortality	RR 0.92 (0.57 to 1.46) LOW
	Major adverse cardiovascular event (MACE) - myocardial infarction	RR 1.12 (0.81 to 1.53) LOW
	Major adverse cardiovascular event (MACE) - revascularisation	RR 0.97 (0.73 to 1.29) MODERATE
	Frequency of adverse events/side-effects - all-cause mortality	RR 0.97 (0.67 to 1.39) MODERATE
GRADE Table 4 (Verschueren et al 2018)	Major adverse cardiovascular event (MACE)	RR 0.69 (0.04 to 10.60) VERY LOW

Exercise therapy vs. care as usual	Frequency of adverse events/side-effects	Not pooled (2.8% intervention vs. 2.8% control) VERY LOW
GRADE Table 5 (Tully & Baumeister 2015)	Major adverse cardiovascular event (MACE) – short to medium term	RR 0.54 (0.31 to 0.95) VERY LOW
Collaborative care vs. care as usual	Major adverse cardiovascular event (MACE) – long-term	RR 1.04 (0.51 to 2.14) VERY LOW
	Frequency of adverse events/side-effects - mortality	RR 1.38 (0.53 to 3.58) VERY LOW

Cardiovascular risk factors

	Outcome	Mean difference (MD) <i>negative values favour intervention</i>
GRADE Table 6 (de Silva et al 2016; Mizuno et al 2014)	Adequacy of control of CVD risk factors – blood pressure	N/A
Metformin vs. placebo	Adequacy of control of CVD risk factors – cholesterol	5.38 lower (26.59 lower to 15.82 higher) VERY LOW
	Cardiovascular disease incidence	N/A
	Frequency of adverse events/side-effects	Narrative Inconsistent results. VERY LOW
GRADE Table 7 (Mizuno et al 2014; Gierisch et al 2013)	Adequacy of control of CVD risk factors – blood pressure	N/A
Aripiprazole vs. placebo	Adequacy of control of CVD risk factors – cholesterol	12.81 lower (19.35 lower to 6.27 lower) VERY LOW
	Cardiovascular disease incidence	N/A
	Frequency of adverse events/side-effects	Narrative. Adverse events appeared higher in intervention group, though this was not statistically tested. VERY LOW

GRADE Table 8 (Teasdale et al 2017; Gierisch et al 2013) Lifestyle interventions vs. care as usual	Adequacy of control of CVD risk factors – systolic blood pressure	0.63 higher (1.86 lower to 3.12 higher) VERY LOW
	Adequacy of control of CVD risk factors – diastolic blood pressure	1.69 lower (3.6 lower to 0.23 higher) VERY LOW
	Adequacy of control of CVD risk factors – cholesterol	0.13 lower (0.29 lower to 0.03 higher) VERY LOW
	Cardiovascular disease incidence	N/A
	Frequency of adverse events/side-effects	Narrative. No severe adverse events observed; however very small sample size. VERY LOW

Evidence to Decision Table

	JUDGEMENT ⁴	EVIDENCE	ADDITIONAL CONSIDERATIONS																														
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	• Cardiovascular disease is considered a main potentially avoidable contributor to excess mortality observed amongst people with SMD. • People with SMD have 1.53 times greater risk of cardiovascular disease and 1.85 times greater risk of death due to cardiovascular disease. • Complex interplay - combination of several NCDs, such as diabetes, hypertension and CVD, and the presence of a severe mental disorder. • The use of antipsychotic medications has been associated in recent years with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death See Background section for further details.																															
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?⁵ cardiovascular disease <table><tr><td></td><td>Anti-depressants</td><td>Psychosocial</td><td>Exercise</td><td>Collaborative care</td></tr><tr><td>Trivial</td><td></td><td></td><td></td><td></td></tr><tr><td>Small</td><td></td><td></td><td></td><td></td></tr><tr><td>Moderate</td><td></td><td></td><td></td><td></td></tr><tr><td>Large</td><td></td><td></td><td></td><td></td></tr><tr><td>Varies</td><td></td><td></td><td></td><td></td></tr></table>		Anti-depressants	Psychosocial	Exercise	Collaborative care	Trivial					Small					Moderate					Large					Varies					The anticipated effects were as follows for the different interventions: 5.1 Cardiovascular disease • Anti-depressants: Very small effect in opposite directions from two different systematic reviews for MACE compared to care as usual, which were both not statistically significant. Very small effect in favour of intervention for frequency of adverse events / side-effects, which was not statistically significant. • Psychosocial interventions: Very small effect sizes for several types of MACE and for frequency of adverse events / side-effects compared to care as usual, none of which were statistically significant. A further systematic Cochrane review (Richards et al 2017) on psychological interventions for coronary heart disease reported the following results: Cardiac mortality: 11 studies, n=4792, RR 0.79 (0.63 to 0.98), LOW GRADE; non-fatal myocardial infarction: 13 studies, n=7845, RR 0.82 (0.64 to 1.05), LOW GRADE; revascularization: 13 studies, n=6822, RR 0.94 (0.81 to 1.11), MODERATE GRADE; total mortality: 23 studies, n=7776, RR	No systematic reviews have looked at aggregate scores of cardiovascular risk (including blood pressure, cholesterol, weight gain etc.), which is a limitation.
	Anti-depressants	Psychosocial	Exercise	Collaborative care																													
Trivial																																	
Small																																	
Moderate																																	
Large																																	
Varies																																	

⁴ These were made based on the available evidence and/or the GDG's expertise.

⁵ Please note that where interventions had already been excluded as possible recommendation, these were not considered further, and have therefore been shaded out.

	Don't know				
	cardiovascular risk				
		Metformin	Aripiprazole	Lifestyle	
	Trivial				
	Small				
	Moderate				
	Large				
	Varies				
	Don't know				
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?				
	cardiovascular disease				
		Anti-depressants	Psychosocial	Exercise	Collaborative care
	Trivial				
	Small				
	Moderate				
	Large				
	Varies				

0.90 (0.77 to 1.05), MODERATE GRADE.
• Exercise therapy: Moderate effect in favour of intervention compared to care as usual for MACE, which was not statistically significant. No significant differences between groups for frequency of adverse events / side-effects. • Collaborative care: Substantial and statistically significant effect in favour of intervention compared to care as usual for MACE in the short to medium term. Small effects in favour of care as usual for MACE in the long-term and frequency of adverse events / side-effects, which were both not statistically significant.
5.2 Cardiovascular risk
• Metformin: Substantial effect in favour of intervention compared to placebo for adequacy of control of CVD risk factors (cholesterol), but which was not statistically significant. Inconsistent results for frequency of adverse events/side-effects. Other outcomes not reported. A further 3 systematic reviews (Agarwal et al 2017; Liu et al 2015; Gierisch et al 2013, 2014) reported no significant differences between groups for adverse effects. • Aripiprazole: Substantial effect in favour of intervention compared to placebo for adequacy of control of CVD risk factors (cholesterol), which was statistically significant. Adverse events appeared higher in intervention group, though this was not statistically tested. Other outcomes not reported. Another systematic review (Zimbron et al 2016) also found a significant effect on LDL cholesterol across two studies. • Lifestyle interventions: Inconsistent results for different types of adequacy of control of CVD risk factors, none of which were statistically significant. No severe adverse events observed; however very small sample size. Cardiovascular disease incidence not reported. Another meta-analysis by Gierisch et al (2013, 2014) also found no significant effect on lipid levels or total cholesterol for behavioural interventions compared to care as usual.

CERTAINTY OF EVIDENCE	<table><tr><td>Don't know</td><td></td><td></td><td></td><td></td></tr></table> cardiovascular risk <table><tr><td></td><td>Metformin</td><td>Aripiprazole</td><td>Lifestyle</td></tr><tr><td>Trivial</td><td></td><td></td><td></td></tr><tr><td>Small</td><td></td><td></td><td></td></tr><tr><td>Moderate</td><td></td><td></td><td></td></tr><tr><td>Large</td><td></td><td></td><td></td></tr><tr><td>Varies</td><td></td><td></td><td></td></tr><tr><td>Don't know</td><td></td><td></td><td></td></tr></table>	Don't know						Metformin	Aripiprazole	Lifestyle	Trivial				Small				Moderate				Large				Varies				Don't know					
	Don't know																																			
		Metformin	Aripiprazole	Lifestyle																																
	Trivial																																			
	Small																																			
	Moderate																																			
	Large																																			
	Varies																																			
	Don't know																																			
	What is the overall certainty of the evidence of effects? cardiovascular disease <table><tr><td></td><td>Anti-depressants</td><td>Psychosocial</td><td>Exercise</td><td>Collaborative care</td></tr><tr><td>Very low</td><td></td><td></td><td></td><td></td></tr><tr><td>Low</td><td></td><td></td><td></td><td></td></tr><tr><td>Moderate</td><td></td><td></td><td></td><td></td></tr><tr><td>High</td><td></td><td></td><td></td><td></td></tr><tr><td>No included studies</td><td></td><td></td><td></td><td></td></tr></table> cardiovascular risk		Anti-depressants	Psychosocial	Exercise	Collaborative care	Very low					Low					Moderate					High					No included studies					5.1 Cardiovascular disease • Anti-depressants: VERY LOW certainty • Psychosocial interventions: LOW and MODERATE certainty • Exercise therapy: VERY LOW certainty • Collaborative care: VERY LOW certainty 5.2 Cardiovascular risk • Metformin: VERY LOW certainty • Aripiprazole: VERY LOW certainty • Lifestyle interventions: VERY LOW certainty				
	Anti-depressants	Psychosocial	Exercise	Collaborative care																																
Very low																																				
Low																																				
Moderate																																				
High																																				
No included studies																																				

	<table border="1"> <tr> <td></td><td>Metformin</td><td>Aripiprazole</td><td>Lifestyle</td></tr> <tr> <td>Very low</td><td></td><td></td><td></td></tr> <tr> <td>Low</td><td></td><td></td><td></td></tr> <tr> <td>Moderate</td><td></td><td></td><td></td></tr> <tr> <td>High</td><td></td><td></td><td></td></tr> <tr> <td>No included studies</td><td></td><td></td><td></td></tr> </table>		Metformin	Aripiprazole	Lifestyle	Very low				Low				Moderate				High				No included studies					
	Metformin	Aripiprazole	Lifestyle																								
Very low																											
Low																											
Moderate																											
High																											
No included studies																											
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability	The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012).																									
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? PICO 5.1 – cardiovascular disease	5.1 Cardiovascular disease • Anti-depressants: Insufficient evidence. • Psychosocial interventions: Evidence does not favour the intervention or the comparator. • Exercise therapy: Insufficient evidence. • Collaborative care: Some low-quality evidence in favour of the intervention in the short to medium-term, but not is not the case in the long-term. Results need to be																									

	Anti-depressants	Psychosocial	Exercise	Collaborative care
Favors the comparison				
Probably favors the comparison				
Does not favor either the intervention or the comparison				
Probably favors the intervention				
Favors the intervention				
Varies				
Don't know				

cardiovascular risk

treated with caution.

5.2 Cardiovascular risk

- **Metformin:** Insufficient evidence.
- **Aripiprazole:** Evidence not sufficiently, though there is an indication in favour of the intervention, which needs to be treated with caution.
- **Lifestyle interventions:** Insufficient evidence.

		Metformin	Aripiprazole	Lifestyle		
	Favors the comparison					
	Probably favors the comparison					
	Does not favor either the intervention or the comparison					
	Probably favors the intervention					
	Favors the intervention					
	Varies					
	Don't know					

RESOURCES REQUIRED

How large are the resource requirements (costs)?

cardiovascular disease

	Anti-depressants	Psychosocial	Exercise	Collaborative care
Large costs				
Moderate costs				
Negligible costs				
Varies				
Don't know				

cardiovascular disease

From WHO Pen (2010):

Condition	Intervention	Target population	Cost effectiveness
Congestive heart failure	ACE inhibitor and betablocker with diuretics in district hospital	Adults	150 US\$/DALY
Stroke and ischemic and hypertensive heart disease	Combination treatment with aspirin, betablocker, thiazide, ACE inhibitor and statin in district hospital	Adults	2128 US\$/DALY
Stroke	Aspirin dose within 48 hours of onset of acute stroke	Adults over 15	149 US\$/DALY
Myocardial infarction and stroke	Combination treatment with aspirin, betablocker, thiazide and ACE inhibitor for secondary prevention in district hospital	Adults	409 US\$/DALY
Myocardial infarction	Aspirin and betablocker for acute management	Adults	14 US\$/DALY
Ischemic heart disease	Aspirin, betablocker with optional ACE inhibitor for secondary prevention in district hospital	Adults	688 US\$/DALY
Ischemic heart disease	Statin incremental to aspirin, betablocker and ACE inhibitor for secondary prevention in district hospital	Adults	2028 US\$/DALY

Of the pharmacological interventions included in this review, the following are included in the WHO Essential Medicines List (EML):

- **Anti-depressants:** Unclear, as drugs not specified in systematic reviews.
- **Metformin:** Included in EML, as treatment for diabetes.
- **Aripiprazole:** Not included in EML.

The resource requirements for the pharmacological interventions is likely to be lower than for the non-pharmacological interventions (due to the elevated training and human resource costs associated with non-pharmacological interventions), though of the included pharmacological interventions only metformin is included in the WHO EML.

	<table> <tr> <td></td><td>Metformin</td><td>Aripiprazole</td><td>Lifestyle</td></tr> <tr> <td>Large costs</td><td></td><td></td><td></td></tr> <tr> <td>Moderate costs</td><td></td><td></td><td></td></tr> <tr> <td>Negligible costs</td><td></td><td></td><td></td></tr> <tr> <td>Varies</td><td></td><td></td><td></td></tr> <tr> <td>Don't know</td><td></td><td></td><td></td></tr> </table>		Metformin	Aripiprazole	Lifestyle	Large costs				Moderate costs				Negligible costs				Varies				Don't know					
	Metformin	Aripiprazole	Lifestyle																								
Large costs																											
Moderate costs																											
Negligible costs																											
Varies																											
Don't know																											
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High X No included studies	None identified.																									

COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies X No included studies	None identified.																					
EQUITY	What would be the impact on health equity? cardiovascular disease <table><tr><td></td><td>Anti-depressants</td><td>Psychosocial</td><td>Exercise</td><td>Collaborative care</td></tr><tr><td>Reduced</td><td></td><td></td><td></td><td></td></tr><tr><td>Probably reduced</td><td></td><td></td><td></td><td></td></tr><tr><td>Probably no impact</td><td></td><td></td><td></td><td></td></tr></table>		Anti-depressants	Psychosocial	Exercise	Collaborative care	Reduced					Probably reduced					Probably no impact					None identified.	
	Anti-depressants	Psychosocial	Exercise	Collaborative care																			
Reduced																							
Probably reduced																							
Probably no impact																							

Probably increased				
Increased				
Varies				
Don't know				

cardiovascular risk

	Metformin	Aripiprazole	Lifestyle
Reduced			
Probably reduced			
Probably no impact			
Probably increased			
Increased			
Varies			
Don't know			

ACCEPTABILITY	Is the intervention acceptable to key stakeholders?					None identified.	
	cardiovascular disease						
		Anti-depressants	Psychosocial	Exercise	Collaborative care		
	No						
	Probably no						
	Probably yes						
	Yes						
	Varies						
	Don't know						
	cardiovascular risk						

		Metformin	Aripiprazole	Lifestyle
	No			
	Probably no			
	Probably yes			
	Yes			
	Varies			
	Don't know			
FEASIBILITY	Is the intervention acceptable to key stakeholders?	Studies for the different interventions have been conducted in the following countries:		
	cardiovascular disease	5.1 Cardiovascular disease • Anti-depressants: Netherlands and other unspecified countries • Psychosocial interventions: USA and Canada. • Exercise therapy: USA and Canada • Collaborative care: USA 5.2 Cardiovascular risk • Metformin: Venezuela, China, Sri Lanka, USA • Aripiprazole: USA and Austria • Lifestyle interventions: unclear See box for costs on which medications are included in the WHO EML.		

No				
Probably no				
Probably yes				
Yes				
Varies				
Don't know				

PICO 5.1 – cardiovascular risk

	Metformin	Aripiprazole	Lifestyle
No			
Probably no			
Probably yes			
Yes			
Varies			
Don't know			

For the non-pharmacological interventions, although intervention features, such as duration or frequency, could possibly be adapted for each particular setting, e.g. by being administered by suitably trained and supported non-specialists, there is no direct evidence available to support this.

WHO guidelines for general population

Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings Geneva, WHO, 2010. http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

One of NCD prevention/control priority conditions, in focus of the Global NCD Action Plan

Primary prevention of heart attacks and strokes:

- Tobacco cessation, Regular physical activity 30 minutes a day, Reduced intake of salt <5 g per day, Fruits and vegetables at least 400g per day
- Aspirin, statins and antihypertensives for people with 10 year cardiovascular risk >30%
- Antihypertensives for people with blood pressure $\geq 160/100$
- Antihypertensives for people with persistent blood pressure $\geq 140/90$ and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures

Acute myocardial infarction:

- Aspirin

Secondary prevention (post myocardial infarction):

- Tobacco cessation, healthy diet and regular physical activity
- Aspirin, angiotensin-converting enzyme inhibitor, beta-blocker, statin

Secondary prevention (post stroke):

- Tobacco cessation, healthy diet and regular physical activity.
- Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin

Secondary prevention (Rheumatic heart disease):

- Regular administration of antibiotics to prevent streptococcal pharyngitis and recurrent acute rheumatic fever

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GDG Recommendations

For people with severe mental disorder (SMD) and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

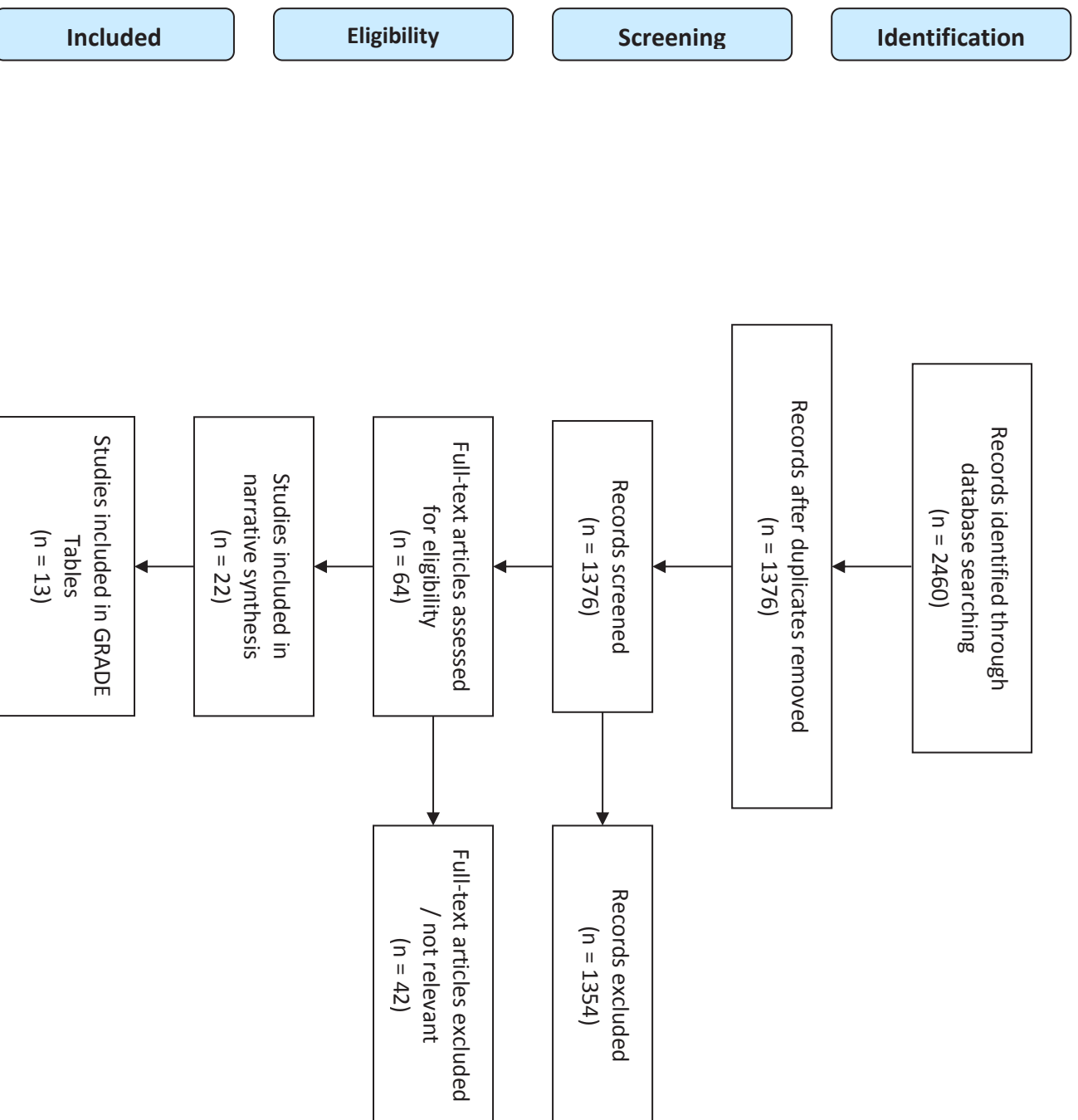
RECOMMENDATION	Recommendations: Recommendation 1: For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the <i>WHO Package of Essential Noncommunicable Disease Interventions</i> (WHO PEN) for primary care in low-resource settings (2010) for lowering cardiovascular risk and management of cardiovascular disease. (<i>Strength of recommendation: Strong; Quality of evidence: High to Moderate for different interventions</i>). Recommendation 2: For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended: a) Behavioural lifestyle (healthy diet, physical activity) interventions may be considered these interventions should be appropriate and tailored to the needs of this population. (<i>Strength of recommendation: Conditional; Quality of evidence: Very low</i>). b) Collaborative care, i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-ups, and enhanced inter-professional communication, may be considered for cardiovascular disease management. (<i>Strength of recommendation: Conditional; Quality of evidence: Very low</i>). Recommendation 3: For people with severe mental disorders and cardiovascular risk factors, the following is recommended: a) Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. (<i>Strength of</i>
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	<i>recommendation: Conditional; Quality of evidence: Very low).</i> <u>Best practice</u> for people with severe mental disorders and pre-existing cardiovascular disease: ○ Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects. ○ Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects. Best practice for people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors: ○ Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.
JUSTIFICATION	For people with SMD and pre-existing cardiovascular disease Pharmacological interventions: • There is insufficient evidence to recommend the prescribing of antidepressants (or one class of antidepressant over another) in people with pre-existing cardiovascular disease or in those who have suffered from acute coronary syndrome events, in the reduction of MACE (<i>Quality of the evidence: very low</i>). Non-pharmacological / psychosocial interventions: • There is insufficient evidence to recommend the use of psychological therapies (e.g. CBT) compared to care as usual, to support the reduction of MACE in people with depression and comorbid coronary heart disease (<i>Quality of the evidence: Low to moderate</i>). • There is insufficient evidence to recommend the use of exercise therapy compared to standard medical treatments or other interventions (e.g. group counselling) for the reduction of MACE, in people with depression and comorbid cardiovascular disease (<i>Quality of the evidence: Very low</i>). Collaborative care:

	- There is some evidence to indicate that collaborative care compared to care as usual in people with comorbid depression and coronary heart disease may be associated with a relative and absolute reduction in MACE events in the short to medium-term (less than 12 months; however note all studies were conducted in the USA). There is insufficient evidence to indicate whether MACE events are less likely in the longer-term (over 12 months) or adverse events are lower in collaborative care vs. care as usual models (<i>Quality of the evidence: Very low</i>). For people with SMD and cardiovascular risk factors Pharmacological interventions: - There is insufficient evidence to recommend the prescribing of metformin versus placebo for the control of total cholesterol (<i>Quality of the evidence: Very low</i>). - Aripiprazole compared to placebo may be associated with a lowering of total cholesterol, although usage should be balanced against potential side effects, including possible serious side effects (<i>Quality of evidence: Very low</i>). Lifestyle interventions: - At present the evidence is insufficient on the usage of lifestyle interventions for the management of systolic and diastolic blood pressure and total cholesterol in populations with SMD (<i>Quality of the evidence: Very low</i>). However, a conditional recommendation has been made, as there is a strong recommendation by WHO for the general population; there are benefits of the intervention on other non-communicable disease outcomes; and there is a low risk of associated adverse events.
SUBGROUP CONSIDERATIONS	All of the systematic reviews and meta-analyses included in this document for comorbid cardiovascular disease focused on interventions for persons with depression. No reviews were included which assessed interventions in populations SMD (e.g. schizophrenia, bipolar disorder) with comorbid cardiovascular disease. The evidence and recommendations are therefore indirect for populations with SMD and comorbid cardiovascular disease. Evidence relating to collaborative care models all derived from US-based studies of people with depression and comorbid cardiovascular disease may have limited generalizability outside of this context.
IMPLEMENTATION CONSIDERATIONS	No remarks.
MONITORING AND EVALUATION	No remarks.

RESEARCH PRIORITIES	• Better quality randomised controlled trials of interventions (psychosocial and pharmacological) for the prevention of major adverse cardiovascular events in people with SMD (e.g. schizophrenia-spectrum disorders) and pre-existing cardiovascular disease, preferably conducted over multi-sites. • Randomised controlled trials which assess interventions that are known to be effective in populations without SMD (hypertension and total cholesterol control) are needed in SMD populations. • Studies which specifically address cardiac side effects of psychotropic medications in SMD would be beneficial (e.g. Clozapine-induced tachycardia). • Studies which assess implementation of interventions in low- and middle-income settings. • Studies which assess cost-effectiveness of interventions.
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**PRISMA Flow Diagram for systematic review of the reviews:
SMD and cardiovascular disease/risk**



EVIDENCE PROFILE

DIABETES MELLITUS

PICO QUESTION: For people with severe mental disorder (SMD) and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

Background on the PICO question

There is high co-morbidity between SMD and diabetes mellitus.

Several systematic reviews have looked at prevalence and risk of diabetes for people with SMD (Pillinger et al 2017), which have reported pooled prevalence rates of around 10%; for example Vancampfort et al (2016) estimated prevalence rates of diabetes to be 11.3% for people with SMD overall, and other systematic reviews estimated prevalence rates to be 13% on average (ranging between 1.3% and 50% across studies) for people with psychosis (Ward & Druss 2015), 9.5% to 10.75% in people with schizophrenia (Stubbs et al 2015), 9.4% in people with bipolar disorder (Vancampfort et al 2015a), and 8.7% in people with depression (Chen et al 2016), though individual studies may show wide variation (Naskar et al 2017). The risk of developing diabetes has been found to be around double in people with SMD such as schizophrenia and bipolar disorder (Charles et al 2016, Stubbs et al 2015, Vancampfort et al 2015a), and around 1.5 times the risk in people with depression (Chen et al 2016, Rotella & Manucci 2013, Vancampfort et al 2015b, Yu et al 2015). Part of this increased risk may be explained by the elevated risk of diabetes associated with some medications used by people with SMD, such as some (but not all) anti-psychotics (Correll et al 2015, Vancampfort et al 2016, Zhang et al 2017), or anti-depressants (Rotella & Manucci 2013), though results for the latter are inconsistent (Barnard et al 2013; Correll et al 2015); lithium may also play a role (Vancampfort). Aside from medications, other factors including health-related behaviours (such as physical activity and diet) and other environmental factors may be associated (Vancampfort). An elevated risk has also been demonstrated for women compared to men (Naskar et al 2017; Vancampfort et al 2016), and there may also be a differential association with age (Chen et al 2016; Naskar et al 2017), and symptom severity in people with schizophrenia (Perry et al 2017).

In addition, people with diabetes are at a higher risk of developing SMD, though these may often go undetected. For example, a two-fold increase in depression rates have been reported in people with diabetes (Abrahamian et al 2016). Hasan et al (2016) found that comorbid depression among people with diabetes affected approximately a fifth of the diabetic population globally (23.36%), though there were wide-ranging differences in studies conducted in developed and developing regions of the world regarding the burden of comorbid depression among people with diabetes; there was a higher burden of comorbid depression in people living in developing regions (26.32%), in women (15.41%), and when assessed by self-report scales

(SRS) (22.66%). Other systematic reviews have similarly suggested that comorbid depression among people with diabetes may be higher in low- and middle-income countries than in high-income countries (Mendenhall et al 2014).

These high co-morbidity rates between SMD and diabetes result in an increased risk of mortality for people with SMD. For example, Ribe et al (2014) found that overall mortality rate ratios for persons with SMD and diabetes were 4.14 for men and 3.13 for women; the cumulative risks of death within 7 years of diabetes diagnosis for persons with SMD and diabetes were 15.0% for those younger than 50 years, 30.7% (95% CI 27.8– 33.4%) for those aged 50–69 years, and 63.8% (95% CI 58.9–68.2%) for those aged 70 years or older. Among persons suffering from both diseases, 33.4% of natural deaths were attributed to diabetes and 14% of natural deaths were attributed to the interaction between diabetes and SMD. Vinogradova et al (2010) reported that schizophrenia and bipolar disorder both significantly increased risk of death after adjusting for age and gender, with hazard ratios for schizophrenia of 1.84 (95% CI 1.42–2.40) and for bipolar disorder of 1.51 (95% CI 1.10– 2.07). After adjusting for the other factors, hazard ratios were 1.52 (95 CI 1.17–1.97) for schizophrenia and 1.47 (95% CI 1.07–2.02) for bipolar disorder. In addition, around a 1.5 to 2-fold risk of mortality has been shown for people with co-morbid depression and diabetes (Engelmann et al 2016; Hofmann et al 2013, Park et al 2013, Van Dooren et al 2013).

This document covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD and diabetes mellitus. Those outcomes were included, which were considered to be critical diabetes-related outcomes. The inclusion of interventions was guided by the research evidence available for people with diabetes and SMD.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Population: People with SMD and diabetes mellitus

Intervention:

- Pharmacological interventions: e.g. medication to treat diabetes
- Non-pharmacological interventions: e.g. behavioural lifestyle interventions, cognitive behaviour therapy

Comparison: One treatment versus another or care as usual

Outcomes:

- Critical:
 - Fasting blood glucose <120mg/dl; post-prandial blood glucose <160mg/dl
 - Glycosylated haemoglobin A1c (HbA1c <7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
 - Diabetes complications – MACE, chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important:
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Li C et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for patients with diabetes and depression. *Journal of Psychosomatic Research*. 2017; 95: 44-54

McBain H et al. Self management interventions for type 2 diabetes in adult people with severe mental illness. *Cochrane Database of Systematic Reviews*. 2016;4

Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549

EXCLUDED FROM GRADE TABLES

Atlantis E et al. Collaborative care for comorbid depression and diabetes: A systematic review and meta-analysis. BMJ Open. 2014; 4(4): e004706

Baumeister H et al. Psychological and pharmacological interventions for depression in patients with diabetes mellitus: An abridged Cochrane review. Diabetic Medicine. 2014; 31(7): 773-786

Baumeister H et al. Psychological and pharmacological interventions for depression in patients with diabetes mellitus. 2012; Cochrane Database of Systematic Reviews, Issue 12. Art. No.: CD008381

Baxter AJ et al. Reducing excess mortality due to chronic disease in people with severe mental illness: Meta-review of health interventions. British Journal of Psychiatry. 2016; 208(4)

Cezaretto A et al. Impact of lifestyle interventions on depressive symptoms in individuals at-risk of, or with, type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2016. 26(8): 649-62

Chapman et al. Psychological Interventions for the Management of Glycemic and Psychological Outcomes of Type 2 Diabetes Mellitus in China: A Systematic Review and Meta-Analyses of Randomized Controlled Trials. Frontiers in public health. 2015; 3: 252

Charova E et al. Web-based interventions for comorbid depression and chronic illness: a systematic review. J Telemed Telecare. 2015; 21(4): 189-201

Cooper SJ et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol. 2016; 30(8): 717-48

Gierisch JM et al. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. AHRQ Comparative Effectiveness Reviews. 2013

Gierisch JM et al. Pharmacologic and Behavioral Interventions to Improve Cardiovascular Risk Factors in Adults With Serious Mental Illness: A Systematic Review and Meta-Analysis. J Clin Psychiatry 2014;75(5):e424–e440

Huang Y et al. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. BMC Psychiatry. 2013; 13:260

Jeeva F et al. Is treatment of depression cost-effective in people with diabetes? A systematic review of the economic evidence. Int J Technol Assess Health Care. 2013; 29(4): 384-91

- Pascoe MC et al. Psychosocial interventions and wellbeing in individuals with diabetes mellitus: A systematic review and meta-analysis. *Frontiers in Psychology*. 2017; 8:14
- Robinson DJ et al. Diabetes and mental health. *Can J Diabetes*. 2013; 37 Suppl 1: S87-92
- Roopan S & Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: A systematic review. *Acta Neuropsychiatrica*. 2017; 29(3): 127-139
- Sharp J et al. Computerized cognitive behaviour therapy for depression in people with a chronic physical illness. *British Journal of Health Psychology*. 2013; 18(4): 729-744
- Smith SM et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev*. 2016; 3: CD006560-CD006560
- Uchendu C & Blake H. Effectiveness of cognitive-behavioural therapy on glycaemic control and psychological outcomes in adults with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetic Medicine*. 2017; 34(3): 328-339
- van Eck van der Sluijs JF et al. Illness burden and physical outcomes associated with collaborative care in patients with comorbid depressive disorder in chronic medical conditions: A systematic review and meta-analysis. *General Hospital Psychiatry*. 2018; 50: 1-14
- Van Der Heijden MMP et al. Effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in type 2 diabetes mellitus: A systematic review. *Diabetologia*. 2013; 56(6): 1210-1225
- Watson LC et al. Practice-based interventions addressing concomitant depression and chronic medical conditions in the primary care setting: a systematic review and meta-analysis. *J Prim Care Community Health*. 2013; 4(4): 294-306
- Whiteman KL et al. Systematic review of integrated general medical and psychiatric self-management interventions for adults with serious mental illness. *Psychiatric Services*. 2016; 67(11): 1213-1225
- Xie J & Deng W. Psychosocial intervention for patients with type 2 diabetes mellitus and comorbid depression: A meta-analysis of randomized controlled trials. *Neuropsychiatric Disease and Treatment*. 2017; 13: 2681-2690

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Diabetes medication vs. placebo	Fasting blood glucose	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any pharmacological interventions) high-quality systematic review.
		HbA1c		
		Diabetes complications	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
2	Weight loss medications vs. placebo	Fasting blood glucose	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any pharmacological interventions) high-quality systematic review.
		HbA1c		
		Diabetes complications	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
3	Anti-psychotic switching vs. placebo or care as usual	Fasting blood glucose	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any pharmacological interventions) high-quality systematic review.
		HbA1c		
		Diabetes complications	No relevant systematic review available.	N/A

		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
4	Weight loss and diabetes medications combined vs. placebo or care as usual	Fasting blood glucose	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any pharmacological interventions) high-quality systematic review.
		HbA1c		
		Diabetes complications	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
5	Non-pharmacological (behavioural) interventions vs. care as usual	Fasting blood glucose	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any non-pharmacological interventions) high-quality systematic review.
		HbA1c	Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549	The most recent comprehensive (i.e. SMD overall; any non-pharmacological interventions) high-quality systematic review; provides a combined analysis for non-pharmacological interventions.
		Diabetes complications	No relevant systematic review available.	N/A

		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
6	Cognitive behaviour therapy vs. care as usual	Fasting blood glucose	Li C et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for patients with diabetes and depression. Journal of Psychosomatic Research. 2017; 95: 44-54	The most recent high-quality systematic review available on CBT (i.e. which includes a separate analysis for CBT) and diabetes, but for people with depression (rather than SMD).
		HbA1c		
		Diabetes complications	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A
7	Self-management interventions vs. care as usual plus information	Fasting blood glucose	No relevant systematic review available.	N/A
		HbA1c	McBain H et al. Self management interventions for type 2 diabetes in adult people with severe mental illness. Cochrane Database of Systematic Reviews. 2016;4	The most recent high-quality (Cochrane) systematic review available on self-management interventions for people with SMD.
		Diabetes complications	No relevant systematic review available.	N/A
		Frequency of adverse events/side-effects	No relevant systematic review available.	N/A

Narrative description of the studies that went into analysis¹

Taylor et al (2017) conducted a systematic review and meta-analysis to determine the clinical effectiveness of pharmacological and non-pharmacological (behavioural) interventions for improving glycaemic control in people with SMD. A systematic literature search was performed on 30/10/2015 to identify randomised controlled trials (RCTs) in adults with SMD, with or without a diagnosis of diabetes that measured fasting blood glucose or glycated haemoglobin (HbA1c). Screening and data extraction were carried out independently by two reviewers. The authors used random effects meta-analysis to estimate effectiveness, and subgroup analysis and univariate meta-regression to explore heterogeneity. The Cochrane Collaboration's tool was used to assess risk of bias. 54 eligible RCTs were found in 4,392 adults (40 pharmacological, 13 behavioural, one mixed intervention). Data for meta-analysis were available from 48 RCTs (n = 4052). Both pharmacological (mean difference (MD), -0.11mmol/L; 95% confidence interval (CI), [-0.19, -0.02], p = 0.02, n = 2536) and behavioural interventions (MD, -0.28mmol/L; 95% CI, [-0.43, -0.12], p<0.001, n = 956) were effective in lowering fasting glucose, but not HbA1c (pharmacological MD, -0.03%; 95% CI, [-0.12, 0.06], p = 0.52, n = 1515; behavioural MD, 0.18%; 95% CI, [-0.07, 0.42], p = 0.16, n = 140) compared with usual care or placebo. In subgroup analysis of pharmacological interventions, metformin and antipsychotic switching strategies improved HbA1c. Behavioural interventions of longer duration and those including repeated physical activity had greater effects on fasting glucose than those without these characteristics. Baseline levels of fasting glucose explained some of the heterogeneity in behavioural interventions but not in pharmacological interventions. Although the strength of the evidence is limited by inadequate trial design and reporting and significant heterogeneity, the authors concluded that there is some evidence that behavioural interventions, antipsychotic switching, and metformin can lead to clinically important improvements in glycaemic measurements in adults with SMD. However, when only including studies that did not exclude patients with diabetes in the meta-analysis, of the pharmacological interventions only anti-psychotic switching was statistically significant for the HbA1c outcome.

Li et al (2017) conducted a meta-analysis to systematically examine the efficacy of cognitive behavior therapy (CBT) for diabetic patients who have comorbid depression and to identify which aspects can be improved through intervention. Methods: A systematic literature review was performed using multiple databases. The inclusion criteria included randomized controlled trials (RCTs) of CBT that were conducted with diabetes patients with clinically relevant depression. Results: Ten RCTs, with a total sample size of 998 participants, met the inclusion criteria. Compared with control groups, the CBT groups had statistically significant, long-term improvements in depression (standardized mean differences [SMD] = - 0.65, 95% confidence interval [CI] (- 0.98 to - 0.31), P = 0.0002), quality of life (SMD = 0.29, 95%CI (0.08 to 0.51), P = 0.007), fasting glucose (SMD = 0.21, 95%CI (0.04 to 0.37), P = 0.01) and anxiety (SMD = - 0.49, 95%CI (- 0.88 to - 0.10), P = 0.01). No improvements were found in glycemic control or in diabetes-related distress. Authors' conclusions: The results of this meta-analysis showed that CBT can be effective in reducing depression symptoms and fasting glucose in diabetes patients with comorbid depression as well as in improving quality of life and anxiety in the long-term. The results showed that CBT can serve as a promising treatment alternative for diabetes patients with comorbid depression.

¹ Please note that this section includes the abstracts as taken directly from the publications.

McBain et al (2016) conducted a Cochrane systematic review to assess the effects of diabetes self-management interventions specifically tailored for people with type 2 diabetes and severe mental illness. The date of the last search of all databases was 07 March 2016. Randomised controlled trials of diabetes self management interventions for people with type 2 diabetes and severe mental illness were included. Main results: One randomised controlled trial involving 64 participants with schizophrenia or schizoaffective disorder was included. Investigators evaluated the 24-week Diabetes Awareness and Rehabilitation Training (DART) programme in comparison with usual care plus information (UCI). Follow-up after trial completion was six months. Risk of bias was mostly unclear but was high for selective reporting. Trial authors did not report on diabetes-related complications, all-cause mortality, adverse events, health-related quality of life nor socioeconomic effects. Twelve months of data on self care behaviours as measured by total energy expenditure showed a mean of 2148 kcal for DART and 1496 kcal for UCI (52 participants; very low-quality evidence), indicating no substantial improvement. The intervention did not have a substantial effect on glycosylated haemoglobin A1c (HbA1c) at 6 or 12 months of follow-up (12-month HbA1c data 7.9% for DART vs 6.9% for UCI; 52 participants; very low-quality evidence). Researchers noted small improvements in body mass index immediately after the intervention was provided and at six months, along with improved weight post intervention. Diabetes knowledge and self efficacy improved immediately following receipt of the intervention, and knowledge also at six months. The intervention did not improve blood pressure. Authors' conclusions: Evidence is insufficient to show whether type 2 diabetes self management interventions for people with severe mental illness are effective in improving outcomes. Researchers must conduct additional trials to establish efficacy, and to identify the active ingredients in these interventions and the people most likely to benefit from them.

GRADE Evidence Tables²

Table 1: Diabetes medication for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: March 2018

Question: Diabetes medication compared to placebo for people with SMD and diabetes mellitus

Setting: mental health inpatients and outpatients

Bibliography: Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	diabetes medication	placebo	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) (negative values favour diabetes medication)												
3 ^a	randomised trials	very serious ^b	serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	68	68	-	mean difference 0.3 lower (1.12 lower to 0.52 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c (negative values favour diabetes medication)												
3 ^a	randomised trials	very serious ^g	not serious	serious ^d	serious ^h	publication bias strongly suspected ^f	73	80	-	mean difference 0.11 lower (0.31 lower to 0.09 higher)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

² See Annex 5, page **XX** for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	diabetes medication	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- a. Two of these studies assessed metformin, and 1 assessed rosiglitazone. All studies were conducted in Venezuela. All participants had either schizophrenia, schizoaffective disorder or bipolar disorder, and were also receiving anti-psychotic medication, either clozapine or olanzapine. See Table 1 in Taylor et al 2017.
- b. This has been rated as very serious, as all included studies had an unclear risk of bias in the masking of the outcome assessment but all fulfilled the other two criteria used. This information was taken from Table S2 of Taylor et al 2017, and from the individual studies included in the systematic review.
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 50% by Taylor et al 2017 (see Table 3).
- d. This has been rated as serious, as the included studies did not specify whether participants had diabetes or not in the eligibility criteria.
- e. This has been rated as serious, as the overall number of included individuals is low (i.e. between 100 and 200), the confidence interval includes 'no effect' (i.e. crosses 0), and there is appreciable benefit and harm. This information was taken from Table 3 of Taylor et al 2017.
- f. The authors of the systematic review (Taylor et al 2017) produced funnel plots, which indicate potential publication bias. See Figure 4 and Table 4 in Taylor et al 2017.
- g. This has been rated as very serious, as 2 of the included studies had an unclear risk of bias in the masking of the outcome assessment (the other study had incomplete outcome data). This information was taken from Table S2 of Taylor et al 2017, and from the individual studies included in the systematic review.
- h. This has been rated as serious, as the overall number of included individuals is low (i.e. between 100 and 200), and the confidence interval includes 'no effect'. This information was taken from Table 3 of Taylor et al 2017.

Table 2: Weight loss medication for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: March 2018

Question: Weight loss medication interventions compared to placebo for people with SMD and diabetes mellitus

Setting: mental health inpatients and outpatients

Bibliography: Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549.

doi:10.1371/journal.pone.0168549

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	weight loss medication interventions	placebo	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) (negative values favour weight loss medication)												
3 ^a	randomised trials	very serious ^b	serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	63	64	-	mean difference 0.23 lower (0.77 lower to 0.3 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c (negative values favour weight loss medication)												
3 ^g	randomised trials	very serious ^b	very serious ^h	serious ^d	very serious ⁱ	publication bias strongly suspected ^f	34	32	-	mean difference 0.32 lower (0.84 lower to 0.2 higher)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- a. Two of these studies were conducted in the USA, and 1 in India. One of the studies evaluated sibutramine, 1 study evaluated topiramate, and 1 zonisamide. All participants had either a psychotic disorder such as schizophrenia or schizoaffective disorder, or bipolar disorder, and were also taking anti-psychotic medication, either olanzapine or clozapine. See Table 1 in Taylor et al 2017.
- b. This has been rated as very serious, as the masking of outcome assessment was rated as an unclear risk of bias in all 3 studies (this information was taken from Table S2 in Taylor et al 2017, and from the individual studies included in the systematic review).
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 66% by Taylor et al 2017 (see Table 3).
- d. This has been rated as serious, as the included studies did not specify whether participants had diabetes or not in the eligibility criteria.
- e. This has been rated as serious, as the overall number of included individuals is low (i.e. between 100 and 200), the confidence interval includes 'no effect', and there is appreciable benefit. This information was taken from Table 3 of Taylor et al 2017.
- f. The authors of the systematic review (Taylor et al 2017) produced funnel plots, which indicate potential publication bias. See Figure 4 and Table 4 in Taylor et al 2017.
- g. Two of these studies were conducted in the USA, and 1 in Austria. All 3 of the studies evaluated sibutramine. All participants had either schizophrenia or schizoaffective disorder, and were also taking anti-psychotic medication, e.g. olanzapine or clozapine. See Table 1 of Taylor et al 2017.
- h. This has been rated as very serious, as heterogeneity (I²) was reported to be 86% by Taylor et al 2017 (see Table 3).
- i. This has been rated as very serious, as the overall number of included individuals is very low (i.e. below 100), the confidence interval includes 'no effect', and there is appreciable benefit. This information was taken from Table 3 of Taylor et al 2017.

Table 3: Anti-psychotic switching for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: March 2018

Question: Anti-psychotic switching compared to placebo or care as usual for SMD and diabetes mellitus

Setting: mental health inpatients and outpatients

Bibliography: Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549.
doi:10.1371/journal.pone.0168549

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-psychotic switching	placebo or care as usual	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) (negative values favour anti-psychotic switching)												
7 ^a	randomised trials	very serious ^b	serious ^c	serious ^d	not serious	publication bias strongly suspected ^e	375	354	-	mean difference 0.04 lower (0.25 lower to 0.17 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c (negative values favour anti-psychotic switching)												
6 ^f	randomised trials	very serious ^b	not serious ^g	serious ^d	not serious	publication bias strongly suspected ^e	323	309	-	mean difference 0.11 lower (0.18 lower to 0.05 lower)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- a. Five of these studies assessed switching to aripipazole, and 2 assessed switching to orally disintegrating olanzapine. Three studies were conducted in the US, 1 in Japan, 1 in India, and 2 studies included several countries (in Europe, North America and Africa). All participants had either schizophrenia, schizoaffective disorder, schizophreniform or bipolar disorder, or other related psychotic disorders. Four studies used placebo as a comparator, and 3 studies used care as usual as comparator. See Table 1 of Taylor et al 2017.
- b. This has been rated as very serious, as all studies were reported to have an unclear risk of bias for the masking of the outcome assessment (this information was taken from Table S2 in Taylor et al 2017).
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 51% by Taylor et al 2017 (see Table 3).
- d. This has been rated as serious, as the included studies did not specify whether participants had diabetes or not in the eligibility criteria.
- e. The authors of the systematic review (Taylor et al 2017) produced funnel plots, which indicate potential publication bias. See Figure 4 and Table 4 in Taylor et al 2017.
- f. Three of these studies assessed switching to aripipazole, 2 assessed switching to orally disintegrating olanzapine, and 1 study assessed switching to quetiapine. Four studies were conducted in the US, 1 in Japan, and 1 study was conducted in several countries (Canada, Netherlands, US and Mexico). All participants had either schizophrenia, schizoaffective disorder, schizophreniform or bipolar disorder, or other related psychotic disorders. Three studies used placebo as a comparator, and 3 studies used care as usual as comparator. See Table 1 of Taylor et al 2017.
- g. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Taylor et al 2017 (see Table 3).

Table 4: Weight loss and diabetes medications combined for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: March 2018

Question: Weight loss and diabetes medications combined compared to placebo or care as usual for people with SMD and diabetes mellitus

Setting: mental health inpatients and outpatients

Bibliography: Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549.

doi:10.1371/journal.pone.0168549

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	weight loss and diabetes medications combined	placebo or care as usual	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) (negative values favour weight loss / diabetes medications)												
2 ^a	randomised trials	very serious ^b	very serious ^c	very serious ^d	serious ^e	publication bias strongly suspected ^f	162	65	-	mean difference 0.04 higher (0.47 lower to 0.56 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c (negative values favour weight loss / diabetes medications)												
2 ^a	randomised trials	very serious ^b	not serious ^g	very serious ^d	not serious	publication bias strongly suspected ^f	162	65	-	mean difference 0.02 lower (0.24 lower to 0.2 higher)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- a. One of these 2 studies assessed metformin plus sibutramine, and the other assessed adjunctive treatment algorithms that included amantadine, metformin and zonisamide. One study was conducted in Venezuela, and 1 study included several countries (Israel, Mexico, Korea, Russia, and USA). All participants had either schizophrenia or schizoaffective disorder. One study used placebo as a comparator, and 1 study used care as usual (olanzapine) as comparator. See Table 1 in Taylor et al 2017.
- b. This has been rated as very serious, as both studies were reported to have an unclear risk of bias for masking of outcome assessment. This information was taken from Table S2 in Taylor et al 2017.
- c. This has been rated as very serious, as heterogeneity (I²) was reported to be 83% by Taylor et al 2017 (see Table 3).
- d. This has been rated as very serious, as one of the studies excluded people with diabetes, and the other did not specify in its inclusion criteria whether participants had diabetes or not.
- e. This has been rated as serious, as the confidence interval includes 'no effect', and there is appreciable harm. This information was taken from Table 3 of Taylor et al 2017.
- f. The authors of the systematic review (Taylor et al 2017) produced funnel plots, which indicate potential publication bias. See Figure 4 and Table 4 in Taylor et al 2017.
- g. This has been reported as not serious, as heterogeneity (I²) was reported to be 8% by Taylor et al 2017 (see Table 3).

Table 5: Non-pharmacological (behavioural) interventions for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Non-pharmacological (behavioural) interventions compared to care as usual for people with SMD and diabetes mellitus

Setting: inpatients and outpatients

Bibliography:

Taylor J, Stubbs B, Hewitt C et al. The effectiveness of pharmacological and non-pharmacological interventions for improving glycaemic control in adults with severe mental illness: A systematic review and meta-analysis. PLOS ONE. 2017; 12(1): e0168549. doi:10.1371/journal.pone.0168549

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	non-pharmacological (behavioural) interventions	Care as usual	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) (negative values favour non-pharmacological interventions)												
7 ^a	randomised trials	very serious ^b	serious ^c	serious ^d	not serious	publication bias strongly suspected ^e	354	324	-	mean difference 0.28 lower (0.53 lower to 0.03 lower)	⊕○○○ VERY LOW	CRITICAL
HbA1c (negative values favour non-pharmacological interventions) ¹												
3 ^f	randomised trials	very serious ^g	not serious	serious ^d	serious ^h	publication bias strongly suspected ^e	75	65	-	mean difference 0.18 higher (0.07 lower to 0.42 higher)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

- a. 2 of these studies defined the intervention as a lifestyle intervention, 2 as physical exercise, 2 as weight-loss interventions, and 1 as dietary control and physical activity. 3 studies were conducted in the USA, and 1 in Sweden, Canada, Netherlands and Taiwan respectively. The control group was care as usual in most studies; 1 study included occupational therapy as comparator and 1 study an aesthetic study circle. All participants had either schizophrenia, schizoaffective disorder or bipolar disorder, or another psychiatric diagnosis. Participants in at least 6 of the studies were also taking anti-psychotic medication. See Table 1 of Taylor et al 2017.
- b. This has been rated as very serious, as 4 of the 7 studies had an unclear risk of bias for masking of outcome assessment, and 2 of the studies had drop-out rates of over 30%. This information was taken from Table S2 in Taylor et al 2017, and from the individual studies included in the systematic review.
- c. This has been rated as serious, as heterogeneity (I²) was reported to be 61% by Taylor et al 2017 (see Table 3).
- d. This has been rated as serious, as the included studies did not specify whether participants had diabetes or not in the eligibility criteria.
- e. The authors of the systematic review (Taylor et al 2017) produced funnel plots, which indicate potential publication bias. See Figure 4 and Table 4 in Taylor et al 2017.
- f. All 3 studies defined the intervention as a lifestyle intervention. The studies were conducted in the USA, Sweden and Switzerland (1 country each). All participants had either schizophrenia, schizoaffective disorder or bipolar disorder, or another psychiatric diagnosis. See Table 1 in Taylor et al 2017.
- g. This has been rated as very serious, as all 3 studies had an uncertain risk of bias for the masking of outcome assessment, and 1 of the studies had uneven drop-out rates. This information was taken from Taylor et al 2017.
- h. This has been rated as serious, as the number of participants is low.

Table 6: Cognitive behaviour therapy (CBT) for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Cognitive behaviour therapy (CBT) compared to care as usual for people with SMD and diabetes mellitus

Setting: not specified

Bibliography: Li C et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for patients with diabetes and depression. Journal of Psychosomatic Research. 2017; 95: 44-54

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behavioural therapy (CBT)	care as usual	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) - post-intervention (negative values favour CBT)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behavioural therapy (CBT)	care as usual	Relative (95% CI)	Absolute (95% CI)		
3 ^a	randomised trials	serious ^b	not serious ^c	serious ^d	serious ^e	publication bias strongly suspected ^f	84	91	-	MD 0.63 lower (0.94 lower to 0.33 lower)	⊕○○○ VERY LOW	CRITICAL
HbA1c - post-intervention (negative values favour CBT) ¹												
7 ^g	randomised trials	serious ^b	serious ^h	serious ^d	serious ⁱ	publication bias strongly suspected ^f	381	378	-	MD 0.22 lower (0.53 lower to 0.08 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c - short-term (under 6 months) (negative values favour CBT)												
5 ^j	randomised trials	serious ^b	serious ^k	serious ^d	serious ⁱ	publication bias strongly suspected ^f	148	155	-	MD 0.3 lower (0.71 lower to 0.1 higher)	⊕○○○ VERY LOW	CRITICAL
HbA1c - long-term (over 6 months) (negative values favour CBT)												
6 ^l	randomised trials	serious ^b	serious ^m	serious ^d	not serious	publication bias strongly suspected ^f	358	347	-	MD 0.19 lower (0.47 lower to 0.09 higher)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events / side-effects - not reported												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	cognitive behavioural therapy (CBT)	care as usual	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

- a. One study was conducted in Taiwan, 1 in China, and 1 in the USA. All participants had either a psychiatric diagnosis of depression or met clinical criteria on a validated depression scale. Two of the studies included CBT only, and 1 included CBT plus motivational interviewing; all studies had care as usual as control group. The intervention lasted 2 months, 3 months and 6 months in the 3 studies respectively. See Li et al 2017 (Table 1).
- b. This has been rated as serious, as one of the studies had a high risk of bias for masking of outcome assessment. This information was taken from Figure 3 in Li et al 2017, and from the individual studies included in the systematic review.
- c. This has been rated as not serious, as heterogeneity (I²) was reported to be 0% by Li et al 2017 (see Figure 11).
- d. This has been rated as serious, as participants with depression were included, rather than SMD.
- e. This has been rated as serious, as the total number of participants is low.
- f. Funnel plots were not produced by the authors of the systematic review (Li et al 2017) due to the small number of studies, but the authors of the systematic review state that publication bias is likely. See page 52 in Li et al 2017.
- g. Four studies were conducted in the USA, 1 in Taiwan, 1 in Germany, and 1 in Iran. All participants had either a psychiatric diagnosis of depression or met clinical criteria on a validated depression scale. Five of the studies included CBT only (of which 1 was diabetes-specific CBT, and 1 was specific to depression/adherence), 1 included CBT plus motivational interviewing, and 1 included telephone CBT plus walking. Five studies had care as usual as control group, and 2 diabetes education. The intervention lasted between 2 and 12 months in studies. See Li et al 2017.
- h. This has been rated as serious, as heterogeneity (I²) was reported to be 74% by Li et al 2017 (see Figure 7).
- i. This has been rated as serious, as the confidence interval includes both 'no effect' and appreciable benefit.
- j. Three studies were conducted in the USA, 1 in Taiwan, and 1 in Iran. All participants had either a psychiatric diagnosis of depression or met clinical criteria on a validated depression scale. Four of the studies included CBT only (of which 1 was diabetes-specific CBT, and 1 was specific to depression/adherence), and 1 included CBT plus motivational interviewing. Four studies had care as usual as control group, and 1 diabetes education. The intervention lasted between 3 and 12 months in studies. See Li et al 2017.
- k. This has been rated as serious, as heterogeneity (I²) was reported to be 67% by Li et al 2017 (see Figure 8).
- l. Four studies were conducted in the USA, 1 in Germany, and 1 in Iran. All participants had either a psychiatric diagnosis of depression or met clinical criteria on a validated depression scale. Five of the studies included CBT only (of which 1 was diabetes-specific CBT, and 1 was specific to depression/adherence), and 1 included telephone CBT plus walking. Four studies had care as usual as control group, and 2 diabetes education. The intervention lasted 6 months in 3 studies, and 12 months in 3 studies. See Li et al 2017.
- m. This has been rated as serious, as heterogeneity (I²) was reported to be 65% by Li et al 2017 (see Figure 8).

Table 7: Self-management interventions for people with SMD and diabetes mellitus

Author(s): Maya Semrau (first rater), Jayati Das-Munshi (second rater)

Date: April 2018

Question: Self-management interventions compared to care as usual plus information for people with SMD and diabetes mellitus

Setting: community

Bibliography: McBain H et al. Self-management interventions for type 2 diabetes in adult people with severe mental illness. Cochrane Database of Systematic Reviews. 2016;4

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	self-management interventions	care as usual plus information	Relative (95% CI)	Absolute (95% CI)		
Fasting blood glucose (mmol/L) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
HbA1c (negative values favour diabetes medication) (follow up: mean 6 months)												
1 ^a	randomised trials	serious ^b	not serious	not serious	very serious ^c	publication bias strongly suspected ^d	26	26	-	mean difference 0.01 lower (0 to 0)	⊕○○○ VERY LOW	CRITICAL
Diabetes complications - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Frequency of adverse events/side-effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval

Explanations

a. The study was conducted in San Diego in the USA. The intervention included basic diabetes education, nutrition, and lifestyle exercise. See pages 16 & 29 in McBain et al 2016.

b. This has been rated as serious, as the risk of bias was unclear for masking of outcome assessment. This information was taken from page 66 in McBain et al 2016.

c. This has been rated as very serious, as the number of participants is very low, and the effect was reported by the authors not to be statistically significant. The confidence intervals do not seem to be reported. See page 4 in McBain et al 2016.

d. The authors of the systematic review (McBain et al 2016) reported high risk of reporting bias, as not all outcomes that were measured were included in the paper. See page 31 in McBain et al 2016.

Additional evidence not mentioned in GRADE tables³

Anti-depressants in people with depression and diabetes

Two systematic reviews have been conducted on the use of anti-depressants in people with depression that included diabetes-related outcomes. However, one of these was out-of-date and the other was of low quality so that they could not be included in the GRADE evidence tables.

1. Baumeister et al (2012, 2014) conducted a Cochrane review on pharmacological interventions (anti-depressants) in people with depression and diabetes mellitus, which included HbA1c as outcome. The searches for this systematic review were conducted in December 2011. The meta-analysis indicated a beneficial effect of SSRIs versus placebo with a MD for HbA1c of -0.4% (95% CI -0.6 to -0.1; P = 0.002; 238 participants; five trials). The between-study heterogeneity was low ($I^2 = 0\%$). This evidence was given a MODERATE GRADE for quality of evidence by the authors. 1 trial comparing fluoxetine with paroxetine did not report sufficient information to compute effect sizes, 1 trial comparing magnesium supplementation with imipramine did not find significant differences, 1 trial comparing fluoxetine with citalopram reported a benefit in favour of fluoxetine (MD for HbA1c -1.0%; 95% CI -1.9 to -0.2; N = 40). This evidence was given a LOW GRADE for quality of evidence by the authors. In regards to adverse effects, no significant differences were found between nortriptyline and placebo / serious adverse effects were rarely reported. No significant difference was found between imipramine and magnesium supplementation / serious adverse effects were rarely reported. This evidence was given a LOW GRADE for quality of evidence by the authors.
2. Roopen & Larsen (2017) conducted a systematic review to evaluate antidepressants most suitable for patients with depression and comorbid DM. Both randomised, controlled double-blind trials and non-randomised-controlled trials were included. In total, 18 articles were included. Results: The combination of depression and DM may be harmful as depression has a strong impact on psychosocial and medical outcomes in patients with DM. Almost all of the trials in this review showed a reduction in depressive symptoms after treatment with an antidepressant in the acute as well as during maintenance phase. It showed that depression improvement had a favourable effect on glycaemic control that was weight independent. Some studies included only subjects with minor depression or with suboptimal-controlled diabetes making it difficult to show an effect. Authors' conclusions: From these data, they recommended choosing a selective serotonin reuptake inhibitor (SSRI) if possible to treat depression among patients with diabetes. If treatment with a tricyclic antidepressant is needed, closer glycaemic monitoring is recommended. Bear in mind that there is a possible risk of hypoglycemia when using SSRIs. Agomelatine and bupropion have shown promising results, but need to be investigated in more trials. *Please note that this review was rated to be of low quality according to AMSTAR.*

Psychological and pharmacological interventions in people with depression and diabetes

Baumeister et al (2012/2014) conducted a Cochrane systematic review and meta-analysis on psychological and pharmacological interventions for depression in patients with diabetes mellitus. Randomized controlled trials investigating psychological and pharmacological interventions for depression in adults with diabetes and depression were included. A comprehensive search of primary studies according to Cochrane were conducted. Primary outcomes were depression and glycaemic control. Further, treatment adherence, diabetes complications, mortality, healthcare costs and quality of life were investigated. Two reviewers identified primary studies and extracted data independently. Random-effects model meta-analyses were conducted to compute overall estimates of treatment outcomes. The database search resulted in 3963 references, of which 19 trials were

³ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

included. Randomized controlled trials of psychological interventions showed positive effects on short- and medium-term depression severity [standardized mean difference short-term range -1.47; -0.14, n = 7; medium-term standardized mean difference -0.42 (95% CI -0.70 to -0.14), n = 3] and depression remission [odds ratio short term 2.88 (95% CI 1.58-5.25), n = 4; odds ratio medium term 2.49 (95% CI 1.44-4.32), n = 2]. Effects on glycaemic control in psychological intervention trials varied substantially (standardized mean difference range -0.97 to 0.47, n = 4). Selective serotonin reuptake inhibitors showed a moderate beneficial effect on short-term depression severity [standardized mean difference -0.39 (95% CI -0.64 to -0.13), n = 5] and depression remission [odds ratio 2.52 (95% CI 1.11-5.75), n = 2]. Glycaemic control improved in randomized controlled trials comparing selective serotonin reuptake inhibitors with placebo at the end of treatment [standardized mean difference -0.38 (95% CI -0.64 to -0.12), n = 5]. The authors concluded that psychological and pharmacological interventions positively affect depression outcomes in patients with diabetes at the end of treatment. Furthermore, short-term glycaemic control improved moderately in pharmacological trials. However, most outcomes have not been investigated sufficiently, and there is a lack of follow-up data for pharmacological trials limiting the evidence on the sustainability of treatment effects.

Collaborative care in people with depression and diabetes

Two systematic reviews looked at collaborative care in people with comorbid depression and diabetes, though they are both more than three years old, so were not included in the GRADE evidence tables.

1. Atlantis et al (2014) found seven RCTs, which reported effects on depression outcomes in 1895 participants, and glycated haemoglobin (HbA1c) level in 1556 participants. Collaborative care significantly improved the depression score (standardised mean difference was -0.32 (95% CI -0.53 to -0.11); $I^2=79\%$) and HbA1c level (weighted mean difference was -0.33% (95% CI -0.66% to -0.00%); $I^2=72.9\%$) compared with control conditions. Depression remission did not predict better glycaemic control across studies. The authors concluded that there was limited evidence from short-to-medium term RCTs predominantly conducted in the USA, suggesting that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with comorbid depression and diabetes.

2. Huang et al (2013) found eight studies containing 2,238 patients that met the inclusion criteria. Collaborative care showed a significant improvement in depression treatment response (RR = 1.33, 95% CI = 1.05-1.68), depression remission (adjusted RR = 1.53, 95% CI = 1.11-2.12), higher rates of adherence to antidepressant medication (RR = 1.79, 95% CI = 1.19-2.69) and oral hypoglycemic agent (RR = 2.18, 95% CI = 1.61-2.96), but indicated a non-significant reduction in HbA1c values (MD = -0.13, 95% CI = -0.46-0.19). The authors concluded that improving depression care in diabetic patients is very necessary and important; comparing with usual care, collaborative care was associated with significantly better depressive outcomes and adherence in patients with depression and diabetes.

Relevant guidelines

NICE guidelines *Psychosis and schizophrenia in adults: prevention and management* (Clinical guideline [CG178]; Published date: February 2014 Last updated: March 2014):

- “Physical health”: if person has rapid/excessive weight gain, abnormal lipid levels, or problems with blood glucose management, offer intervention in line with NICE guidance (on obesity, lipid modification, preventing diabetes).

- GPs and primary health care professionals should monitor physical health of people with psychosis; comprehensive health checks and refer to relevant NICE guidance on monitoring cardiovascular disease, diabetes, obesity and respiratory disease.
- Should identify people who have CVD, high blood pressure, abnormal lipid levels, are obese/at risk of obesity, have diabetes/at risk of diabetes (as indicated by abnormal blood glucose levels), or physically inactive, at the earliest opportunity following relevant NICE guidance for these conditions.

NICE guidelines *Bipolar disorder: assessment and management* (Clinical guideline [CG185]; Published date: September 2014 Last updated: February 2016:

- Before starting antipsychotic medication, should measure and record: weight or BMI, pulse, blood pressure, fasting blood glucose or HbA1c blood lipid profile.

NICE guidelines *Depression in adults with a chronic physical health problem: recognition and management* (Clinical guideline [CG91]; Published date: October 2009:

- When prescribing an antipsychotic, monitor weight, lipid and glucose levels, and side effects.

Cooper et al (2016)'s BAP guidelines recommend the following in diabetes management for people with psychosis:

- Potential pre-diabetic states should be investigated and managed as per NICE guidelines for the general population, except that annual screening for this is recommended for those with psychosis receiving antipsychotic medications.
- The prescription of metformin for those not responding to intensive lifestyle interventions needs to be considered in the context of the individual.
- Diabetes should be managed by the general practitioner or a specialist physician, where necessary, as per existing NICE guidelines.
- Dyslipidaemia, especially in the context of a person with diabetes, should be actively managed according to existing NICE guidelines for the general population. There is no contraindication to the prescription of a statin in people prescribed antipsychotics.

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Fluoxetine may increase the potency of hypoglycemics such as **metformin**, **gliclazide**, and **insulin**. Monitor blood glucose control and adjust dosing of hypoglycemics accordingly, especially when starting or stopping fluoxetine. Amitriptyline may increase the potency of sulfonylureas such as **gliclazide**. Monitor blood glucose control and adjust dosing of gliclazide accordingly, especially when starting, stopping, or adjusting amitriptyline doses. Risperidone and clozapine are associated with hyperglycemia and as such, may decrease the efficacy of hypoglycemic medication including **metformin**, **gliclazide**, and **insulin**. Monitor glycemic control and adjust dosing of hypoglycemic medications accordingly.

See Annex for further details.

WHO guidelines for general population

WHO Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010) – Recommendations:

Type 1 diabetes:

- Daily insulin injections

Type 2 diabetes:

- Oral hypoglycemic agents for type 2 diabetes, if glycemic targets are not achieved with modification of diet, maintenance of a healthy body weight and regular physical activity
- Metformin as initial drug in overweight patients and non-overweight
- Other classes of antihyperglycemic agents, added to metformin if glycemic targets are not met
- Reduction of cardiovascular risk for those with diabetes and 10-year cardiovascular risk >20% with aspirin, angiotensin converting enzyme inhibitor and statins

Prevention of onset and delay in progression of chronic kidney disease:

- Optimal glycemic control in people with type 1 or type 2 diabetes
- Angiotensin converting enzyme inhibitor for persistent albuminuria

Prevention of onset and delay of progression of diabetic retinopathy:

- Referral for screening and evaluation for laser treatment for diabetic retinopathy
- Optimal glycemic control and blood pressure control

Prevention of onset and progression of neuropathy:

- Optimal glycemic control

WHO NCD 2012: Guidelines for primary health care in low-resource settings – Recommendations (see next two pages for more details):

- Diagnosing diabetes: point of care devices, if no laboratory services
- Glycaemic control: diet and physical activity as first-line treatment, Metformin as first-line oral hypoglycaemic agent where diet is not sufficient, Sulfonylureas for those patient where metformin is not effective/patient has contraindications
- Reducing the risk of cardiovascular disease and diabetic nephropathy: statins for all people with Type-2 diabetes over 40 years of age, antihypertensive agents to reduce blood pressure, choice of antihypertensive agent
- Prevention of lower limb amputations: educate patients and health care workers
- Prevention of blindness: screening for diabetic retinopathy
- Severe hypoglycaemia, hypoglycaemic emergencies: intravenous hypertonic glucose treatment or glucose (dextrose) for unconscious patients, referral to hospital and drip in emergencies

- Point of care devices can be used in diagnosing diabetes if laboratory services are not available.
Quality of evidence: not graded
Strength of recommendation: strong
- Advise overweight patients to reduce weight by reducing their food intake.
Quality of evidence: very low
Strength of recommendation: conditional
- Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
Quality of evidence: moderate
Strength of recommendation: conditional

- Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g walking).
Quality of evidence: very low
Strength of recommendation: conditional
- Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.
Quality of evidence: very low
Strength of recommendation: strong
- Give sulfonylurea to patients who have contraindications to metformin or in whom metformin does not improve glycaemic control.
Quality of evidence: very low
Strength of recommendation: strong
- Give a statin to all patients with type 2 diabetes aged ≥ 40 years.
Quality of evidence: moderate
Strength of recommendation: conditional
- The target value for diastolic blood pressure in diabetic patients is ≤ 80 mmHg.
Quality of evidence: moderate
Strength of recommendation: strong
- The target value for systolic blood pressure in diabetic patients is < 130 mmHg
Quality of evidence: low
Strength of recommendation: weak
- Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.
Quality of evidence: very low for thiazides, low for ACE inhibitors
Strength of recommendation: strong
- Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.
Quality of evidence: very low
Strength of recommendation: strong

- Give patients health education of patients on foot hygiene, nail cutting, treatment of calluses, appropriate footwear.
Quality of evidence: low
Strength of recommendation: strong
- Educate health care workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation)
Quality of evidence: low
Strength of recommendation: strong
- Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.
Quality of evidence: low
Strength of recommendation: conditional
- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤ 2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.
Quality of evidence: strong
Strength of recommendation: strong
- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤ 2.8 mmol/L administer intravenously 20 to 50 ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon as the patient can ingest food safely.
Quality of evidence: very low
Strength of recommendation: strong
- If blood glucose ≥ 18 mmol (refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital).
Quality of evidence: very low
Strength of recommendation: strong

These recommendations will be the basis for developing simple treatment algorithms for training primary care staff on integrated management of NCDs in low resource-settings.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of findings table (SoF)

	Outcome	Mean difference (MD) (confidence intervals) <i>negative values favour intervention</i>
GRADE Table 1 (Taylor et al 2017) Diabetes medication vs. placebo	Fasting blood glucose (mmol/L)	MD 0.3 lower (1.12 lower to 0.52 higher) VERY LOW
	HbA1c	MD 0.11 lower (0.31 lower to 0.09 higher) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A
GRADE Table 2 (Taylor et al 2017) Weight loss medication vs. placebo	Fasting blood glucose (mmol/L)	MD 0.23 lower (0.77 lower to 0.3 higher) VERY LOW
	HbA1c	MD 0.32 lower (0.84 lower to 0.2 higher) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A
GRADE Table 3 (Taylor et al 2017) Anti-psychotic switching vs. placebo or care as usual	Fasting blood glucose (mmol/L)	MD 0.04 lower (0.25 lower to 0.17 higher) VERY LOW
	HbA1c	MD 0.11 lower (0.18 lower to 0.05 lower) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A

GRADE Table 4 (Taylor et al 2017) Weight loss and diabetes medications combined vs. placebo or care as usual	Fasting blood glucose (mmol/L)	MD 0.04 higher (0.47 lower to 0.56 higher) VERY LOW
	HbA1c	MD 0.02 lower (0.24 lower to 0.2 higher) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A
GRADE Table 5 (Taylor et al 2017) Non-pharmacological (behavioural) interventions vs. care as usual	Fasting blood glucose (mmol/L)	MD 0.28 lower (0.53 lower to 0.03 lower) VERY LOW
	HbA1c	MD 0.18 higher (0.07 lower to 0.42 higher) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A
GRADE Table 6 (Li et al 2017) Cognitive behaviour therapy vs. care as usual	Fasting blood glucose (mmol/L) – post-intervention	MD 0.63 lower (0.94 lower to 0.33 lower) VERY LOW
	HbA1c – post-intervention	MD 0.22 lower (0.53 lower to 0.08 higher) VERY LOW
	HbA1c – short-term (under 6 months)	MD 0.3 lower (0.71 lower to 0.1 higher) VERY LOW
	HbA1c – long-term (over 6 months)	MD 0.19 lower (0.47 lower to 0.09 higher) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A

GRADE Table 7 (McBain et al 2016) Self-management Interventions vs. care as usual plus information	Fasting blood glucose (mmol/L)	N/A
	HbA1c	MD 0.01 lower (0 to 0) VERY LOW
	Diabetes complications	N/A
	Frequency of adverse events / side-effects	N/A

Evidence to Decision Table

	JUDGEMENT ⁴	EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	• There is high co-morbidity between SMD and diabetes mellitus. • People with SMD are at an increased risk of diabetes (around double for schizophrenia and bipolar disorder, and 1.5 times the risk for depression). • People with diabetes are at a heightened risk of SMD (around double for depression), though this is often undetected, with a higher risk in LMICs. • People with comorbid SMD and diabetes have an increased risk of mortality. • There is an association with diabetes for some anti-psychotics, anti-depressants, and lithium. • There is also an association with health-related behaviours (such as physical activity and diet) and other environmental factors, and gender. See Background section for further details.	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?⁵	In regards to desirable anticipated effects, this varied according to the different interventions included in this review: • Diabetes medication: Small effect size in favour of intervention, which was not statistically significant for both fasting blood glucose and HbA1c. • Weight loss medication: Small effect size in favour of intervention, which was not statistically significant for both fasting blood glucose and HbA1c. • Anti-psychotic switching: Small effect size in favour of intervention for both fasting blood glucose and HbA1c, which was statistically significant for HbA1c but not for fasting blood glucose. • Weight loss and diabetes medications combined: Very small effect size, in favour of placebo/care as usual for fasting blood glucose and in favour of	There is clinical trial evidence to support the effectiveness of collaborative care. The TEAMcare study improved depression AND diabetes outcomes among primary care patients with poorly-controlled

⁴ These were made based on the available evidence and/or the GDG's expertise

⁵ Please note that where interventions had already been excluded as possible recommendation, these were not considered further, and have therefore been shaded out.

	Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management
Trivial							
Small							
Moderate							
Large							
Varies							
Don't know							

- intervention for HbA1C, both of which were not statistically significant.
- Non-pharmacological interventions combined: Moderate effect size, in favour of intervention for fasting blood glucose, which was statistically significant, and a small effect size in favour of care as usual for HbA1c, which was not statistically significant.
 - Cognitive behaviour therapy: Moderate effect sizes in favour of intervention for both fasting blood glucose and HbA1c (in the short- and long-term), though this was only statistically significant for fasting blood glucose.
 - Self-management interventions: No difference between intervention and care as usual plus information for HbA1c. No other outcomes were assessed.

An older Cochrane review (Baumeister et al 2012/2014) found no significant beneficial effects on HbA1c when combined analyses were performed for psychological interventions in the short-, medium- and long-term; the only significant effects were for health education in the short-term, and CBT in the medium-term, though web-based CBT was inferior to waiting-list control in the medium-term; no psychological interventions were effective in the long-term.

Other interventions that have been evaluated for this population include anti-depressants in people with comorbid depression and diabetes, which have reported beneficial effects on diabetes-related outcomes for selective serotonin reuptake inhibitors (SSRIs), though also a possible risk of hypoglycemia when using SSRIs (Baumeister et al 2012/2014; Roopen & Larsen 2017). However, these papers were either of too low quality or too old to be included in the GRADE evidence tables.

Similarly, collaborative care has been found to have a favourable effect (though only statistically significant in one of the papers) on HbA1c in people with comorbid depression and diabetes (Atlantis et al 2014; Huang et al 2013), though these systematic reviews were not sufficiently recent to be included in the GRADE evidence tables.

diabetes and a current major depressive episode after 12 months of treatment (Katon et al 2010)

UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?								In regards to undesirable anticipated effects, diabetes complications and frequency of adverse events / side-effects were not assessed/reported for any of the interventions. However, significant drug-drug interactions with medications used in the treatment of people with SMD have been established for some diabetes medication, such as metformin, gliclazide, and insulin. Also, one of the weight-loss interventions included in this review, sibutramine, has been withdrawn from the UK and elsewhere due to cardiac risks (stroke, MI).	
		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management		
	Trivial									
	Small									
	Moderate									
	Large									
	Varies									
	Don't know									
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects?								The certainty of the evidence of effects was VERY LOW for all interventions and their associated outcomes that were evaluated, including: • Diabetes medication • Weight loss medication • Anti-psychotic switching • Weight loss and diabetes medications combined • Non-pharmacological interventions combined • Cognitive behaviour therapy • Self-management interventions	

VALUES AND PREFERENCES										
		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management		
	Very low									
	Low									
	Moderate									
	High									
	No included studies									
	Is there important uncertainty about or variability in how much people value the main outcomes?									
	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability									
	The 2 nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012).									

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?							There is insufficient evidence available to estimate the balance between desirable and undesirable effects for all of the interventions included in this review. This is because diabetes complications and frequency of adverse events / side-effects were not reported for any of the included interventions. However, there are significant drug-drug interactions between several SMD and diabetes medications, and one of the included weight management interventions (sibutramine) has been withdrawn in some countries due to cardiac risks. See box on desirable effects above for effects reported on fasting blood glucose and HbA1c. However, the certainty of the evidence of effects was very low for all included interventions and outcomes.
		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management
	Favors the comparison							
	Probably favors the comparison							
	Does not favor either the intervention or the comparison							
	Probably favors the intervention							
	Favors the intervention							
	Varies							
	Don't know							

RESOURCES REQUIRED	How large are the resource requirements (costs)?	Hutter et al (2010) found that hospitalisation rates and hospitalisation costs, frequency and costs of outpatient visits, emergency department visits, medication costs and total healthcare costs were mainly increased with small to moderate effect sizes in patients with diabetes and comorbid mental disorders compared with diabetic patients without such problems. Of the pharmacological interventions included in this review, the following are included in the essential medicines list (EML): • Diabetes medication: Metformin included in EML, but not rosiglitazone • Weight loss medication: None included in EML (sibutramine, topiramate, zonisamide) • Anti-psychotic switching: None included in EML (aripripazole, olanzapine) • Weight loss and diabetes medication combined: Metformin included in EML, but not sibutramine, amantadine, metformin or zonisamide. The resource requirements for the pharmacological interventions is likely to be lower than for the non-pharmacological interventions (due to the elevated training and human resource costs associated with non-pharmacological interventions), though of the included pharmacological interventions only metformin is included in the essential medicines list.	

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)?								This is not clear for some of the interventions. See boxes above and below.	
		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management		
	Very low									
	Low									
	Moderate									
	High									
	No included studies									

COST EFFECTIVENESS

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

	Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management
Favors the comparison							
Probably favors the comparison							
Does not favor either the intervention or the comparison							
Probably favors the intervention							
Favors the intervention							
Varies							
No included							

From WHO PEN guidelines:

Cost-Effectiveness of Interventions¹⁹

(HIV/AIDS treatment given for comparison)

Condition	Intervention	Target population	Cost effectiveness
HIV/AIDS	Antiretroviral therapy for primary prevention in clinic	All ages	922 US\$/DALY (Sub Saharan Africa)
Ischemic heart disease stroke and Diabetes	Legislation with public education to reduce salt content policy level intervention	All ages	1937 US\$/DALY
Diabetes	Screening of individuals at increased risk for undiagnosed diabetes in clinic	Adults over 25	3870 US\$/QALY
Diabetes	Annual screening for microalbuminuria and treating those who test positive	Adults	3310 US\$/QALY
Diabetes	Life style intervention for type 2 diabetes	Adults	60 US\$/QALY
Diabetes	Optimal Glycemic control in clinic	Adults	1810 US\$/QALY (SSA)
Diabetes	Cholesterol control in clinic	Adults	3330 US\$/QALY (SSA)
Diabetes	Smoking cessation, counselling and medication in clinic	Adolescents and adults	660 US\$/QALY (SSA)
Diabetes	ACE inhibitor for blood pressure control	Adults	620 US\$/QALY (EAP)
Diabetes	Annual eye examination to detect proliferative diabetic retinopathy and macular odema followed by photocoagulation to prevent blindness	Adults	320 US\$/QALY (SSA)

EQUITY	studies																																	
	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know <table><tr><td></td><td>Diabetes medication</td><td>Weight loss medication</td><td>Anti-psychotic switching</td><td>Weight/diabetes medications</td><td>Non-pharmacological</td><td>CBT</td><td>Self-management</td></tr><tr><td>Reduced</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably reduced</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management	Reduced								Probably reduced								Probably								No direct evidence identified.
	Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management																											
Reduced																																		
Probably reduced																																		
Probably																																		

	<table><tr><td>no impact</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably increased</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Increase d</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Varies</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Don't know</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	no impact							Probably increased							Increase d							Varies							Don't know								
no impact																																						
Probably increased																																						
Increase d																																						
Varies																																						
Don't know																																						
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know <table><tr><td></td><td>Diabetes medication</td><td>Weight loss medication</td><td>Anti-psychotic switching</td><td>Weight/diabetes medications</td><td>Non-pharmacological</td><td>CBT</td><td>Self-management</td></tr><tr><td>No</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably no</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>		Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management	No								Probably no								<i>Acceptability to patients</i> Several systematic reviews have looked at adherence to diabetes interventions amongst people with SMD. Two of these (both by Gorczynsk et al 2017a, b) found that a large number of people with schizophrenia were not adhering to their diabetes medication, with adherence rates of between 51%-85%; however adherence rates were higher for people with schizophrenia than those without. Factors that were positively associated with diabetes medication adherence were age, number of outpatient visits, along with multiple medication administration variables. Two other systematic reviews found that depression was associated with lower adherence to diabetes medication as well as diabetes self-care such as dietary and physical activity, as evidenced primarily by descriptive studies; results of intervention studies were reported to be conflicting in both these reviews (Krass et al 2015; Sumlin et al 2014). Of note, drop-out rates were acceptable in all studies that any of the systematic reviews included for all of the interventions, apart from for non-pharmacological (behavioural) interventions combined where there were drop-out rates of above 30% in 2 of the 7 studies. This may indicate (though this was not assessed/reported in the studies) that most of the interventions are considered to be acceptable by the majority of the affected population.												
	Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management																															
No																																						
Probably no																																						

FEASIBILITY	<table><tr><td>Probably yes</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Yes</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Varies</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Don't know</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>								Probably yes								Yes							Varies							Don't know							<i>Acceptability to health care professionals</i> McBain et al (2018) conducted an online cross-sectional survey of 273 health care professionals' (e.g. mental health nurses, psychiatrists) views on diabetes care for people with SMD in the UK, and found that only 25% of respondents had received training in managing type-2 diabetes in people with SMD, and that mental health professionals felt responsible for significantly fewer recommended diabetes care standards than physical health professionals. Significant barriers to its delivery were a lack of knowledge; a need for training in communication and negotiation skills; a lack of optimism about the health of their clients and their ability to manage diabetes in people with SMD; the threat of being discipline; fear of working with people with a mental health condition; a lack of service user engagement; and a need for incentives. The significant enablers were an understanding of the need to tailor treatments and goals for people with SMD.												
	Probably yes																																																	
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	Varies																																																	
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Is the intervention feasible to implement? <table><tr><td></td><td>Diabetes medication</td><td>Weight loss medication</td><td>Anti-psychotic switching</td><td>Weight/diabetes medications</td><td>Non-pharmacological</td><td>CBT</td><td>Self-management</td></tr><tr><td>No</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably no</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Probably yes</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Yes</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>									Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management	No								Probably no								Probably yes								Yes								There have been studies conducted in LMICs (though primarily MICs) for several of the included interventions: • Diabetes medication: Venezuela • Weight loss medication: India (as well as USA) • Anti-psychotic switching: India and countries in Africa (as well as Japan, and countries in Europe and North America) • Weight loss and diabetes medication combined: Venezuela, Mexico and Russia (as well as Israel, Korea and USA) • Non-pharmacological interventions: No LMICs included (USA, Sweden, Canada, Netherlands and Taiwan) • Cognitive behaviour therapy: China (as well as Taiwan and USA) • Self-management interventions: No LMICs (USA only) See above (required resources section) for a list of those pharmacological interventions covered in this review that are included in the essential medicines list (EML).		
	Diabetes medication	Weight loss medication	Anti-psychotic switching	Weight/diabetes medications	Non-pharmacological	CBT	Self-management																																											
No																																																		
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GDG Recommendations

For people with severe mental disorder (SMD) and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

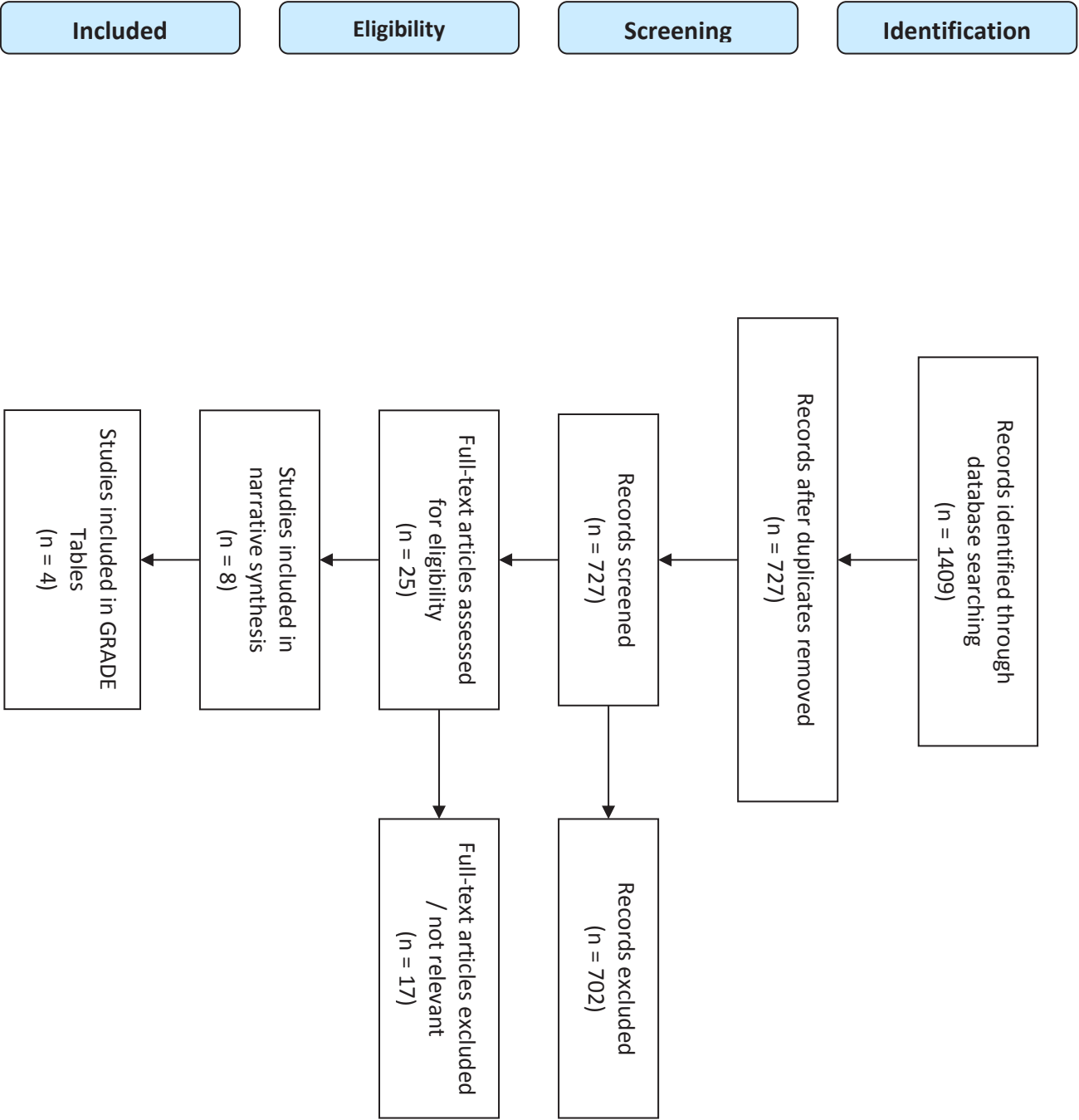
RECOMMENDATION	Recommendations Recommendation 1: For people with severe mental disorders and diabetes, interventions in accordance with the WHO Package of Essential Non-communicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings should be considered for diabetes management (<i>Strength of recommendation: Strong; Quality of evidence: Low</i>). Recommendation 2: Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population. (<i>Strength of recommendation: Strong; Quality of evidence: Very low</i>). Recommendation 3: In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered. (<i>Strength of recommendation: Conditional; Quality of evidence: Very low</i>). Best practice for people with severe mental disorders and diabetes: ○ Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects. ○ Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects. ○ Prescribers should be aware of potential interactions between prescribed medicines for diabetes and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.
JUSTIFICATION	Pharmacological 1. There is at present insufficient evidence to recommend the prescribing of Metformin or Rosiglitazone for

	people with SMD co-prescribed Olanzapine/ Clozapine (<i>Quality of the evidence: Very low</i>). - For the management of weight loss in people with SMD and diabetes mellitus, there is at present insufficient evidence to recommend the prescribing of specific pharmacological interventions (sibutramine, topiramate, and zonisamide reviewed) (<i>Quality of the evidence: Very low</i>). - At present there is insufficient evidence in support of switching antipsychotic medication to Aripiprazole or orally disintegrating Olanzapine (<i>Quality of the evidence: Very low</i>). - There is some limited evidence to indicate switching to Aripiprazole or orally disintegrating Olanzapine may have benefits (<i>Quality of the evidence: Very low</i>). - Weight loss and diabetes mellitus medications combined for people with SMD and comorbid diabetes mellitus: At present there is insufficient evidence to recommend the prescribing of specific adjunctive weight loss medications (medications reviewed included: metformin plus sibutramine, or amantadine, metformin and zonisamide as adjuncts) (<i>Quality of the evidence: Very low</i>). Non-pharmacological interventions - There is some evidence that non-pharmacological interventions show positive effects (<i>Quality of the evidence: Very low</i>). However, a strong recommendation has been made, as there is a strong recommendation by WHO for the general population; there are benefits of the intervention on other non-communicable disease outcomes; and there is a low risk of associated adverse events. - There is some evidence that cognitive behaviour therapy for treatment of depression shows positive effects amongst people with depression and comorbid depression (probably by eliminating the negative effects of depression on diabetes) (<i>Quality of the evidence: Very low</i>). - There is insufficient evidence for self-management interventions (<i>Quality of the evidence: Very low</i>).
SUBGROUP CONSIDERATIONS	No further remarks.
IMPLEMENTATION CONSIDERATIONS	Most of the studies on non-pharmacological interventions have been conducted in high-income countries or upper-middle-income countries.
MONITORING AND EVALUATION	No further remarks.
RESEARCH PRIORITIES	- Research in low- and middle-income settings. - Further research for both pharmacological (including diabetes medications) and non-pharmacological

	interventions specifically amongst people with SMD and diabetes mellitus.
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- | | |
|--|--|
| | <ul style="list-style-type: none">• Further research is encouraged on self-management interventions. |
|--|--|

**PRISMA Flow Diagram for systematic review of the reviews:
SMD and diabetes mellitus**



EVIDENCE PROFILE

HIV/AIDS

PICO QUESTION: For people with severe mental disorder (SMD) and HIV/AIDS, what pharmacological (i.e. ARV drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

Background on the PICO question

The association between mental health problems and HIV and AIDS is complex and bi-directional. International evidence has found that populations with SMD have higher rates of HIV infection. Among persons with SMD, the median prevalence of HIV was 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen et al., 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless (Susser et al., 1993). Additionally, these numbers might also be underestimations, given low rates of medical care attention among those with SMD and high rates of comorbid substance abuse.

Persons with schizophrenia who also have HIV have an over 25-fold risk of dying compared to those who have neither of these (MRR=25.8, 95% CI, 18.8-34.3) (Helleberg et al., 2015).

HIV virus and opportunistic infections associated with AIDS can cause neurological damage, while mental health problems can also arise as a side effect of antiretroviral treatment or from the stigma, stress and socio-economic predicaments associated with the infection and treatment process. In comparison with the general population, people living with HIV are more likely to experience depression, anxiety, suicidality, and substance misuse (Chibanda *et al.* 2016, Hughes *et al.* 2016). In low- and middle-income countries (LMICs), the prevalence of these mental disorders is over 30% in this population. With estimates of 36.9 million people with HIV globally, the burden of disease is significant (UNAIDS 2015). In fact, current predictors indicate that both HIV and AIDS, as well as depression will be the first two leading causes of disability globally by 2030 (Pappin *et al.* 2012).

SMD can also have a detrimental impact on adherence to antiretroviral therapy and progression of AIDS, leading to poorer health outcomes (Uthman et al 2014;Gonzalez et al 2011). Specifically, depression is associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours (Mayston et al., 2012). In a study from Tanzania among about 1,000 women who were HIV-positive, those with depressive symptoms had a higher mortality, HR=2.65 (95% CI, 1.89-3.71) compared to women without depressive symptoms, even after controlling for psychosocial support, sociodemographic variables and clinical condition (Antelman et al., 2007).

People with SMD and HIV experience a complex set of medical, psychological and social complications that need to be tackled through integrated care.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Population: People with SMD and HIV/AIDS

Intervention:

- Pharmacological interventions (e.g. ARV drugs, psychopharmacology)
- Nonpharmacological interventions

Comparison:

- One treatment versus another or care as usual

Outcomes:

- Critical:
 - HIV-related outcomes
- Important:
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Eshun-Wilson I et al. Antidepressants for depression in adults with HIV infection. Cochrane Database of Systematic Reviews. 2018 CD008525

EXCLUDED FROM GRADE TABLES

Hill L & Lee KC. Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. Ann Pharmacother. 2013; 47(1): 75-89

Mayston R et al. Mental disorder and the outcome of HIV/AIDS in low-income and middle-income countries: a systematic review. Aids. 2012; 26(S2): S117-35

Nakimuli-Mpungu E et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. AIDS Behav. 2012; 16(8): 2101-2118

Sharma A et al. S-Adenosylmethionine (SAME) for Neuropsychiatric Disorders: A Clinician-Oriented Review of Research. The Journal of clinical psychiatry. 2017; 78(6): e656-e667

Sherr L et al. HIV and Depression - a systematic review of interventions. Psychology, health & medicine. 2011; 16(5): 493-527

Sin NL & DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. Ann Behav Med. 2014; 47(3): 259-269

Springer SA et al. The impact of DSM-IV mental disorders on adherence to combination antiretroviral therapy among adult persons living with HIV/AIDS: a systematic review. AIDS Behav. 2012; 16(8): 2119-43

Uthman OA et al. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: A systematic review and meta-analysis. Current HIV/AIDS Reports. 2014; 11(3): 291-307

Watkins CC et al. Safety considerations in drug treatment of depression in HIV-positive patients: an updated review. Drug Saf. 2011; 34(8): 623-639

Wright N et al. HIV prevention advice for people with serious mental illness. Cochrane Database of Systematic Reviews. 2016

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Antidepressant vs. placebo	HIV-related outcomes (e.g. mortality, viral suppression, and discontinuation due to adverse drug reactions)	Eshun-Wilson I et al. Antidepressants for depression in adults with HIV infection. Cochrane Database of Systematic Reviews. 2018	Most recent high-quality systematic review, though it looks at depression rather than SMD (no recent suitable systematic review available for SMD). Reports on CD4 change, which is an intermediary outcome.
		Frequency of adverse events / side-effects	Eshun-Wilson I et al. Antidepressants for depression in adults with HIV infection. Cochrane Database of Systematic Reviews. 2018	Most recent high-quality systematic review, though it looks at depression rather than SMD (no recent suitable systematic review available for SMD).

Narrative description of the study that went into analysis¹

Eshun-Wilson et al (2018) conducted a systematic review to assess the efficacy of antidepressant therapy for treatment of depression in PLWH. They searched electronic databases as well as grey literature and reference lists to identify randomized controlled trials of antidepressant drug therapy compared to placebo or another antidepressant drug class. Participants eligible for inclusion had to be aged 18 years and older, from any setting, and have both HIV and depression. Depression was defined according to Diagnostic and Statistical Manual of Mental Disorders or International Statistical Classification of Diseases criteria. Ten studies with 709 participants were included in this review. Of the 10 studies, eight were conducted in high income countries (USA and Italy), seven were conducted prior to 2000 and seven had predominantly men. Seven studies assessed antidepressants versus placebo, two compared different antidepressant classes and one had three arms comparing two antidepressant classes with placebo. Antidepressant therapy may result in a greater improvement in depression compared to placebo. There was a moderate improvement in depression when assessed with the Hamilton Depression Rating Scale (HAM-D) score as a continuous outcome (SMD 0.59, 95% CI 0.21 to 0.96; participants = 357; studies = 6; I² = 62%, low quality evidence). However, there was no evidence of improvement when this was assessed with HAM-D score as a dichotomized outcome (RR 1.10, 95% CI 0.89 to 1.35; participants = 434; studies = 5; I² = 0%, low quality evidence) or Clinical Global Impression of Improvement (CGI-I) score (RR 1.28, 95% CI 0.93 to 1.77; participants = 346; studies = 4; I² = 29%, low quality evidence). There was little to no difference in the proportion of study dropouts between study arms (RR 1.28, 95% CI 0.91 to 1.80; participants = 306; studies = 4; I² = 0%, moderate quality evidence). The methods of reporting adverse events varied substantially between studies, this resulted in very low quality evidence contributing to a pooled estimate (RR 0.88, 95% CI 0.64 to 1.21; participants = 167; studies = 2; I² = 34%; very low quality evidence). Based on this, the authors

¹ Please note that this section includes the abstract as taken directly from the publication.

were unable to determine if there was a difference in the proportion of participants experiencing adverse events in the antidepressant versus placebo arms. However, sexual dysfunction was reported commonly in people receiving selective serotonin reuptake inhibitors (SSRIs). People receiving tricyclic antidepressants (TCAs) frequently reported anticholinergic adverse effects such as dry mouth and constipation. There were no reported grade 3 or 4 adverse events in any study group. There was no evidence of a difference in follow-up CD4 count at study termination (MD -6.31 cells/mm³, 95% CI -72.76 to 60.14; participants = 176; studies = 3; I² = 0%; low quality evidence). Only one study evaluated quality of life score (MD 3.60, 95% CI -0.38 to 7.58; participants = 87; studies = 1; very low quality evidence), due to the poor quality evidence we could not draw conclusions for this outcome. There were few studies comparing different antidepressant classes. It was uncertain if SSRIs differ from TCAs with regard to improvement in depression as evaluated by HAM-D score (MD -3.20, 95% CI -10.87 to 4.47; participants = 14; studies = 1; very low quality evidence). There was some evidence that mirtazapine resulted in a greater improvement in depression compared to an SSRI (MD 9.00, 95% CI 3.61 to 14.39; participants = 70; studies = 1; low quality evidence); however, this finding was not consistent for all measures of improvement in depression for this comparison.

GRADE Evidence Tables²

Table 1. Anti-depressants vs. placebo for people with SMD and HIV/AIDS

Author(s): Maya Semrau (first rater), Neerja Chowdhary (second rater)

Date: April 2018

Question: Anti-depressants (SSRIs) compared to placebo for people with SMD and HIV/AIDS

Setting: outpatients

Bibliography: Eshun-Wilson I et al. Antidepressants for depression in adults with HIV infection. Cochrane Database of Systematic Reviews. 2018 CD008525

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	anti-depressants (SSRIs)	placebo	Relative (95% CI)	Absolute (95% CI)		
HIV-related outcomes - CD4 count (MD above 0 favours antidepressants)												
3 ^a	randomised trials	serious ^d	not serious ^c	serious ^d	very serious ^e	none detected ^f	102	74	-	MD 6.31 lower (72.76 lower to 60.14 higher)	⊕○○○ VERY LOW	CRITICAL
frequency of adverse events / side-effects (RR above 1 favours anti-depressants)												
2 ^g	randomised trials	serious ^h	not serious ⁱ	serious ^d	serious ^j	none detected	61/106 (57.5%)	34/61 (55.7%)	RR 0.88 (0.64 to 1.21)	67 fewer per 1,000 (from 117 more to 201 fewer)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Two of the studies were conducted in the USA, and 1 in South Africa. All 3 studies included participants with MDD (one study also included people with adjustment disorder with depressed mood and a score of over 16 on the HAM-D). The 3 studies included different SSRIs each: escitalopram,

² See Annex 5, page **XX** for a description of the criteria used to grade the quality of evidence (including risk of bias, inconsistency, indirectness, imprecision and reporting bias) in the GRADE evidence tables.

imipramine, fluoxetine (this study also included structured group therapy in both groups). Studies lasted between 6 and 26 weeks. See Eshun-Wilson et al 2018.

b. This has been rated as serious, as one of the studies had an unclear risk of bias for masking of outcome assessment. This information was taken from Figure 10 and the 'characteristics of included studies' tables in Eshun-Wilson et al 2018.

c. This has been rated as not serious, as heterogeneity (I^2) was reported to be 0% by Eshun-Wilson et al 2018 (see Figure 10).

d. This has been rated as serious, as this outcome is considered to be an intermediate rather than a critical outcome for HIV. This has not been rated as very serious, as even though the studies only included people with depression rather than SMD overall, most participants had MDD (so fall under our classification of SMD), and this population is the one that is the most relevant to the intervention, i.e. anti-depressants.

e. This has been rated as very serious, as the number of participants is low, and the confidence intervals include both 'no effect' and appreciable benefit and harm.

f. The authors of the systematic review (Eshun-Wilson et al 2018) did not produce a funnel plot, as there were too few studies. However, the authors of the systematic review concluded that there did not seem to be evidence of reporting bias, as studies with and without substantial treatment effects were identified in the published literature. This information was taken from page 31 in Eshun-Wilson et al 2018.

g. Both studies were conducted in the USA with people with MDD (one of the studies was conducted in HIV positive men who were also receiving psychotherapy). One study included imipramine and the other fluoxetine as intervention. One study lasted for 7 weeks, and the other for 6 weeks with 26-week follow-up. See Eshun-Wilson et al 2018.

h. This has been rated as serious, as both studies had an unclear risk of bias for masking of outcome assessment. This information was taken from the 'characteristics of included studies' table in Eshun-Wilson et al 2018.

i. This has been rated as not serious, as heterogeneity (I^2) was reported to be 34% by Eshun-Wilson et al 2018 (taken from Figure 9).

j. This has been rated as serious, as the number of participants is low, and the confidence intervals include 'no effect'.

Additional evidence not mentioned in GRADE tables³

Drug-drug interactions

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Adjust **dolutegravir** dosing with **carbamazepine**, as carbamazepine may reduce the levels (and efficacy) of dolutegravir. If a patient has not been on integrase strand transfer inhibitors before, it is recommended to double the dose of dolutegravir from 50 mg once a day to twice a day. For patients on a fixed-dose combination of dolutegravir, abacavir, and lamivudine, an extra 50 mg of dolutegravir can be taken 12 hours between doses. If resistance to integrase strand transfer inhibitors is suspected, recommend choosing another mood stabilizing medication over carbamazepine if possible.

Efavirenz has multiple significant interactions with medicines used for SMD. With regards to QT-prolongation: Efavirenz is considered to confer moderate risk of QT interval prolongation. Using efavirenz with other medications that confer risk for QT interval prolongation may significantly elevate the risk of ventricular arrhythmias including torsades de pointes. Advise caution when using **amitriptyline** and **lithium**, which carry indeterminate risk for QT-prolongation and may be risk-modifiers. If used concurrently, monitor for QT-prolongation and arrhythmias on ECG if possible. If able, avoid using efavirenz with **haloperidol**, **risperidone**, **chlorpromazine**, and **clozapine**, as they are all considered to confer moderate risk of QT-interval prolongation. If using one of these medications with efavirenz, monitor for QT-prolongation and arrhythmias on ECG. Avoid using efavirenz with **fluoxetine**, as it is considered to confer high risk of QT interval prolongation. With regards to CNS depression: Concurrent use of efavirenz with **amitriptyline**, **fluphenazine**, or **diazepam** may elevate the risk of CNS depression. With regards to enzymatic induction: Avoid using efavirenz with **carbamazepine**, as these two medications may reduce the levels (and efficacy) of each other. Efavirenz may also reduce the levels of **diazepam**.

There are no significant interactions between **Emtricitabine**, **Lamivudine**, or **Tenofovir disoproxil fumarate (TDF)** and medicines used for SMD.

See Annex for further details.

³ Please note that this section includes text directly taken from the publications, such as lists of recommendations.

Relevant WHO guidelines

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.45). Licence: CC BY-NC-SA 3.0 IGO.

<http://www.who.int/hiv/pub/guidelines/ARV2018update/en/>

RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

1. A DTG based regimen is recommended as a preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- Adults and adolescents (moderate-certainty evidence)
- Women and adolescent girls of childbearing potential (very-low-certainty evidence)

Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential*

- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects, up to eight weeks after conception.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; based on limited data, hormonal contraception and DTG have no reported or expected drug–drug interactions.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV drug guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to eight weeks after conception).

[List of abbreviations: DTG: dolutegravir; EFV efavirenz]

* an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. WHO is taking this potential safety issue seriously and is working closely with all relevant stakeholders to further investigate these preliminary findings. WHO will update these guidelines and provide additional information as it becomes available

Further guidance on the treatment and care of people living with HIV can be found in “*Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd edition 2016.*”

<http://www.who.int/hiv/pub/arv/arv-2016/en/>

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016

http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

Clinical Guidelines: Antiretroviral Therapy	
When to start ART	
When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence). As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).
When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).
What to start: First-line ART	
First-line ART for adults	First-line ART for adults¹ should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI): • TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence). • If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended: ○ AZT + 3TC + EFV ○ AZT + 3TC + NVP ○ TDF + 3TC (or FTC) + NVP (strong recommendation, moderate-quality evidence).
	TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional recommendation, moderate-quality evidence).
	Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
Fixed-dose combination	Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (strong recommendation, moderate-quality evidence).

What ART regime to switch to (second and third line)	
Second-line ART for adults and adolescents	Second-line ART in adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a ritonavir-boosted protease inhibitor (PI). The following sequence of second-line NRTI options is recommended: • After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens. • After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
	Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (strong recommendation, moderate-quality evidence).
	Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (strong recommendation, moderate-quality evidence).
	A heat-stable fixed-dose combination of DRV/r can be used as an alternative boosted PI option for second-line ART (conditional recommendation, low-quality evidence).
A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen (conditional recommendation, low-quality evidence).	
Prevention, screening and management of other comorbidities and chronic care for people living with HIV	
Assessment and management of noncommunicable diseases	Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population¹ (conditional recommendation, very low-quality evidence).
Assessment and management of depression in people living with HIV	Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV (conditional recommendation, very low-quality evidence).
Adherence support interventions	
Recommendation: Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence). The following interventions have demonstrated benefit in improving adherence and viral suppression: • peer counsellors (moderate-quality evidence) • mobile phone text messages (moderate-quality evidence)	

- reminder devices (moderate-quality evidence)
- cognitive-behavioural therapy (moderate-quality evidence)
- behavioural skills training and medication adherence training (moderate-quality evidence)
- fixed-dose combinations and once-daily regimens (moderate-quality evidence).

Considerations in specific populations: People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV

List of abbreviations: 3TC lamivudine; ART antiretroviral therapy; AZT azidothymidine; d4T stavudine; DTG dolutegravir; EFV efavirenz; FTC emtricitabine; NVP nevirapine; TDF tenofovir disoproxil fumarate

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of findings table

	Outcome	Relative risk (RR) <i>values above 1 favour intervention</i>	Mean difference (MD) <i>positive values favour intervention</i>
Antidepressants vs. placebo (GRADE Table 1 ; Eshun-Wilson I et al. 2018)	HIV-related outcomes	N/A	MD 6.31 lower (72.76 lower to 60.14 higher) VERY LOW
	Frequency of adverse events / side-effects	RR 0.88 (0.64 to 1.21) VERY LOW	N/A

Evidence to Decision table

	JUDGEMENT ⁴	EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ✓ ○ Varies ○ Don't know	• Among persons with SMD, the median prevalence of HIV was 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen et al., 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless (Susser et al., 1993). Additionally, these numbers might also be underestimations, given low rates of medical care attention among those with SMD and high rates of comorbid substance abuse. • Persons with schizophrenia who are HIV-positive have an over 25-fold risk of dying compared to those who have neither of these (MRR=25.8, 95% CI, 18.8-34.3) (Helleberg et al., 2015). • There is a large literature on depression and HIV. Specifically, depression symptoms are associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours (Mayston et al., 2012).	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ✓ ○ Varies ○ Don't know	There is no statistically significant effect either in favour of or against antidepressant use on HIV outcomes (in this case CD4 count has been reported - see evidence profile above).	Treatment of HIV in people with SMD is essential. Implementation issues are key in this population. Non-RCT evidence shows that patients with SMD who had successful treatment of HIV patients tended to have less drug use (42% vs. 68%), more ongoing psychiatric visits (70% vs. 58%) and were more

⁴ These were made based on the available evidence and/or the GDG's expertise.

			apt to take psychiatric medicines (70% vs. 40%) (Murphy et al. Community Ment Health J. 2011 Dec;47(6):668-71).
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ✓ ○ Trivial ○ Varies ○ Don't know	The adverse effects of antidepressants are not statistically significant compared to placebo. A number of potential drug-drug interactions exist between ARV and medicines to treat SMD (see section above and Annex).	
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ✓ ○ No included studies	• Effectiveness of treatment for HIV is very robust	The effect is contingent on adherence
VALUES AND PREFERENCES	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ✓	• One study in which a sample of 1028 depressed HIV clients in Uganda was surveyed over 12 months showed that alleviation of major depression is associated with better work-related functioning and productivity, as measured by an increase in number of hours worked. In bivariate analysis, depression alleviation was associated with nearly a doubling of average weekly hours worked. Work-related self-efficacy partially mediated the relationship between depression alleviation and change in hours worked in those with major depression, suggesting that depression (and alleviated or treated depression) influences work functioning in part through its influence on	

		confidence to engage in and successfully perform work-related activities (Wagner et al 2017). • A narrative case study report indicated that people with HIV who received depression care were generally welcoming of treatment and the support of the staff (Odokonyero R 2015). • The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012).									
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ✓ ○ Varies ○ Don't know	<table><tr><td>Benefits</td><td>Harms</td></tr><tr><td>HIV increases mortality in people with SMD. Could expect that treatment should improve HIV-related outcomes (but evidence is lacking from systematic reviews)</td><td>Potential for drug interactions</td></tr><tr><td>Suggestion that integration of services is effective and cost-effective</td><td>Medication side-effects</td></tr><tr><td>Other benefits of treatment of depression in HIV patients since depression associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours</td><td></td></tr></table>	Benefits	Harms	HIV increases mortality in people with SMD. Could expect that treatment should improve HIV-related outcomes (but evidence is lacking from systematic reviews)	Potential for drug interactions	Suggestion that integration of services is effective and cost-effective	Medication side-effects	Other benefits of treatment of depression in HIV patients since depression associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours		
Benefits	Harms										
HIV increases mortality in people with SMD. Could expect that treatment should improve HIV-related outcomes (but evidence is lacking from systematic reviews)	Potential for drug interactions										
Suggestion that integration of services is effective and cost-effective	Medication side-effects										
Other benefits of treatment of depression in HIV patients since depression associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours											

RESOURCES REQUIRED	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ✓ ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Data on HIV and mental health service delivery models indicate that integration supports efficiency and does not increase costs of care. • A narrative review from South Africa and sub-Saharan Africa suggests that integration of mental health care into existing health systems is an effective and cost-efficient approach to expand access to mental health services for people with HIV in resource-limited settings (Jack H et al 2014). • There is also an ongoing study on the cost-effectiveness of screening and treatment of depression among people with HIV in sub-Saharan Africa (Wagner GH et al 2014).	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ✓ ○ High ○ No included studies	No research evidence was identified.	Can draw on indirect evidence on cost of HIV treatment
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies ✓		

EQUITY	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ✓ ○ Varies ○ Don't know	People with SMD are less likely to receive treatment for HIV and other infectious disease. Specifically, depressive symptoms are associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours (Mayston et al., 2012). In a study from Tanzania among about 1,000 women who were HIV-positive, those with DEP symptoms had a higher mortality, HR=2.65 (95% CI, 1.89-3.71), even after controlling for psychosocial support, sociodemographic variables and clinical condition (Antelman et al., 2007).	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ✓ ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Need to consider adherence and dropout problems
FEASIBILITY	Is the intervention feasible to implement? ○ No	• Antidepressants are included in WHO's essential medicine list, though they may not be available in all LMIC settings. • Tools to assist countries in implementation of delivery of mental health services in non-specialised settings exist: e.g. WHO's mhGAP	Psychosocial support is important in addition to medication

	○ Probably no ○ Probably yes ✓ ○ Yes ○ Varies ○ Don't know	Intervention Guide (mhGAP-IG) for mental, neurological and substance use disorders for non-specialist health settings, is a technical tool developed by WHO to assist in implementation of mhGAP. • Initiation of treatment and follow up can be provided as an integrated service for HIV and mental health. Various such models have been described (Leh Hoon Chuah et al, 2017).	
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Relevant parts from WHO guidelines for general population

See section above on WHO guidelines.

GDG Recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the option ○	Conditional recommendation against the option ○	Conditional recommendation for either the option or the comparison ○	Conditional recommendation for the option ○	Strong recommendation for the option ○ ✓
RECOMMENDATION	Recommendation Recommendation 1: For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the WHO updated recommendations on first-line and second-line antiretroviral regimens. (<i>Strength of the recommendation: Strong; Quality of the evidence: Moderate</i>) Recommendation 2: Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. (<i>Strength of the recommendation: Strong; Quality of the evidence: Moderate</i>) Best practice for people with severe mental disorders and HIV/ AIDS: ○ Prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.				
JUSTIFICATION	No reviews were identified for non-pharmacological treatments in people with SMD and comorbid HIV/ AIDS. There is limited RCT evidence for pharmacological treatment in people with SMD and HIV/AIDS. One systematic review that was included in the evidence profile assessed the efficacy of antidepressant therapy for treatment of depression in people with HIV/AIDS. The evidence was of very low quality and the results inconclusive. The drug interaction review reveals multiple interactions between efavirenz and psychotropic medicines, specifically involving the risk of QT interval prolongation, CNS depression and /or enzyme induction. These recommendations are based on indirect evidence of HIV treatment in the general population that are provided in existing WHO guidelines that strongly recommend ARV and adherence management in people with HIV/AIDS with or without SMD. The GDG concluded that the balance between desirable and				

	undesirable effects favor the intervention leading to strong recommendations while noting the need to consider drug interactions. They also concluded that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG also agreed that people with SMD would need additional support for adherence as the very presence of SMD and its associated symptoms can have a detrimental impact on adherence to ARV and progression of AIDS.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	RCTs are required to test the efficacy of the different types of non-pharmacological interventions that exclusively target people with SMD and HIV/AIDS.

Remarks

- No reviews were identified for non-pharmacological treatments in people with SMD and comorbid HIV/ AIDS.
- There is limited RCT evidence for pharmacological treatment in people with SMD and HIV/AIDS

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Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016. http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

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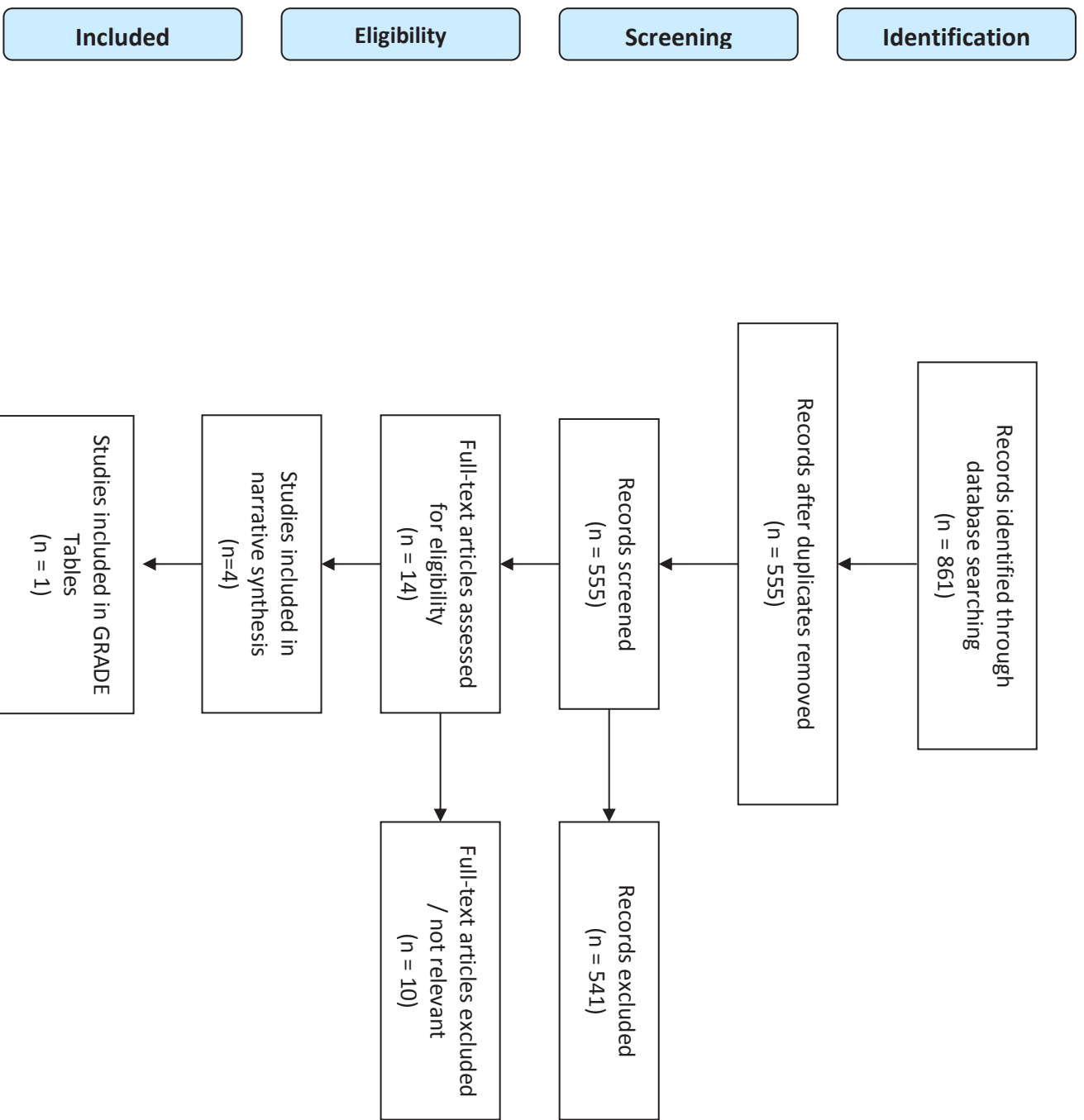
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Wagner GJ, Ghosh-Dastidar B, Robinson E, et al. Effects of Depression Alleviation on Work Productivity and Income Among HIV Patients in Uganda. *International journal of behavioral medicine*. 2017;24(4):628-633. doi:10.1007/s12529-017-9642-7.

PRISMA Flow Diagram for systematic review of the reviews: SMD and HIV



EVIDENCE PROFILE

Other infectious diseases - Tuberculosis, Hepatitis B/C

PICO QUESTION: For people with severe mental disorder (SMD) and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

Background on the PICO question

People with SMD are at greater risk than the general population for exposure to infectious diseases, including tuberculosis (TB) and chronic hepatitis (Rosenberg et al., 2001). Infectious diseases appear to contribute to an increased risk of death in persons with SMD, with a 4- to 8-fold risk of death due to infection compared to the general population. In a systematic review, among persons with schizophrenia the standardized mortality ratio (SMR) for deaths due to infectious diseases was 4.29 (10%-90% quintile, 1.6-7.8) (Saha et al., 2007). Among persons with bipolar disorder, the SMR for deaths due to infectious diseases was 2.25 (95%CI 1.70 - 3.00) (Hayes et al., 2015).

TB and SMD: The link between tuberculosis and SMD is complex and various aspects of this have been described in the literature (Doherty et al., 2013, Kefyalew et al, 2018). Tuberculosis and SMD share common risk factors including homelessness, HIV positive serology, alcohol/substance abuse and migrant status leading to frequent co-morbidity. Patients with SMD are at an increased risk for exposure to tuberculosis infection with higher rates of homelessness, and residence in shelters and group homes. One study, which examined the positive tuberculin tests in a psychiatric day programme, found that 30% of patients with a diagnosis of a depressive illness and 14% of those with a diagnosis of a psychotic illness had positive PPD (purified protein derivative of tuberculosis) results (McQuiston et al., 2001). Another study found an average of 19% positive PPD in admissions to a psychiatric unit (Lopez et al., 1994); 36.7% of men in a homeless hostel with mental illness showed positive PPD results (Saez et al., 1996). In addition to this, patients with SMD often have risk factors for the progression of latent tuberculosis infection (LTBI) to active disease, including smoking, poor nutrition and co-morbidities including diabetes and HIV infection.

There are widespread discriminatory attitudes and behaviours towards patients with TB in the community where they reside. Stigma is an important factor which affects health-related quality of life of people with TB and may contribute to poor TB treatment outcomes, particularly in developing countries. The psychological distress associated with stigma and discrimination may also trigger or aggravate the symptoms of SMD in affected individuals.

In people with SMD and TB, there may be a negative impact on health behaviours such as medication adherence leading to greater morbidity, mortality, amplification of drug-resistance, transmission and all the associated social costs of these outcomes.

Mental health is one of the health services to be integrated under pillar one of the WHO's End TB Strategy 2014, which entails integrated patient-centred care and support (http://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1). It calls for treatment to be provided to all who need it regardless of age, sex, gender or type of TB disease, bacteriological status, co-morbidities or legal status of the patient. The WHO End TB strategy calls to provide TB care through an integrated approach in collaboration with other public health programmes including mental health services such as tailoring TB care delivery models to the specific needs of populations with mental health problems.

Hepatitis B/C and SMD: There is a high prevalence of hepatitis B and C in people with SMD. Among persons with SMD, about 20% have been reported to be infected with hepatitis C (HCV), approximately 11 times that of the population rate (Rosenberg et al., 2001). The prevalence of hepatitis B was 20.2 % (range: 12.5%-49.5%) among persons with SMD in the U.S., with a higher prevalence in inpatient populations, whereas in the overall US adult population the estimated prevalence is 0.3% (Janssen et al., 2015).

There is also evidence that HCV infection itself may be directly associated with psychiatric symptoms, independent of pre-existing psychiatric disorders. Stigmatisation and the fact that patients have to cope with a chronic infectious disorder increases the risk of depression (Schafer A, 2005).

As is seen with TB, mental health problems during antiviral treatment have a strong impact on quality of life, may reduce treatment compliance and are risk factors for treatment failure.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

Population: People with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

Intervention:

- Pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

Comparison:

- One treatment versus another or care as usual

Outcomes:

- Critical
 - Infectious disease-related outcomes

- Important:
 - Frequency of adverse events/side-effects

Search Strategy:

See 'Systematic review search methods' document.

List of systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

None

Additional evidence not mentioned in GRADE tables¹

TB

Doherty AM et al (2013) conducted a comprehensive literature review that examines the complex relationship between tuberculosis and mental illness. Rates of mental illness of up to 70% have been identified in tuberculosis patients. Medications used in the treatment of common mental illnesses, such as depression, may have significant interactions with anti-tuberculosis agents, especially isoniazid and increasingly linezolid. Many medications used in the treatment of tuberculosis can have significant adverse psychiatric effects and some medications such as rifampicin may reduce the effective doses of anti-psychotics by their enzyme induction actions. Treatment with agents such as fluoroquinolones and cycloserine has been associated with mental health disorders, including psychosis. Mental illness and substance abuse may also affect compliance with treatment, with attendant public health concerns. Conclusions: As a result of the common co-morbidity of mental illness and tuberculosis, it is probable that physicians will encounter previously undiagnosed mental illness among patients with tuberculosis. Similarly, psychiatrists are likely to meet tuberculosis among their patients. It is important that both psychiatrists and physicians are aware of the potential for interactions between the drugs used to treat tuberculosis and psychiatric conditions. (Doherty AM et al.)

Alipanah et al (2018) conducted a systematic review and meta-analysis of adherence interventions, including directly observed therapy (DOT), to determine which approaches lead to improved TB treatment outcomes. TB treatment outcomes are improved with the use of adherence interventions, such as patient education and counseling, incentives and enablers, psychological interventions, reminders and tracers, and digital health technologies. Trained healthcare providers as well as community delivery

¹ Please note that this section includes text directly taken from the publications, such as abstracts or lists of recommendations.

provides patient-centered DOT options that both enhance adherence and improve treatment outcomes as compared to unsupervised, self-administered therapy alone.

Hepatitis B/C

Al-Omari A et al (2013) systematically reviewed the evidence of whether pre-emptive antidepressant prophylaxis started before HCV antiviral initiation is beneficial. Inclusion was restricted to RCTs in which prophylactic antidepressant therapy was started at least two weeks before the initiation of HCV antiviral treatment. Six randomized clinical trials involving 522 patients met the inclusion criteria. Although the frequency of on-treatment clinical depression was decreased with antidepressant prophylaxis (risk ratio 0.60 [95% CI 0.38 to 0.93]; $P=0.02$; $I^2=24\%$), no benefit to sustained viral response (SVR) was identified (risk ratio 1.08 [95% CI 0.74 to 1.57]; $P=0.69$; $I^2=58\%$). This practice is not justified to improve SVR in populations free of active depressive symptoms leading up to HCV antiviral therapy. (Al-Omari A et al. Antidepressant prophylaxis reduces depression risk but does not improve sustained virological response in hepatitis C interferon recipients without depression at baseline: a systematic review and meta-analysis. Canadian Journal of Gastroenterology and Hepatology. 2013; 27(10): 575-581)

Drug-drug interactions

Tuberculosis

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Isoniazid can increase valproic acid levels; patients on both medications should be monitored for valproic acid toxicity clinically and via laboratory testing of levels, if possible, especially when starting or stopping isoniazid. Isoniazid can also increase carbamazepine levels and in turn, carbamazepine may increase the hepatotoxicity of isoniazid; patients on both medications should be monitored for clinical signs of carbamazepine toxicity and hepatotoxicity.

Rifampin can decrease the efficacy of amitriptyline, fluoxetine, haloperidol, risperidone, clozapine, valproic acid, carbamazepine, diazepam, and methadone by increasing metabolism. With regards to anti-depressants: Patients on rifampin and either amitriptyline or fluoxetine should be monitored clinically for efficacy of their antidepressant, especially with rifampin dosing changes. With regards to antipsychotics: Consider an alternative antipsychotic medication to haloperidol. Clozapine use with rifampin is not recommended; if it is used, monitor clozapine levels and adjust dosing as needed. Patients on rifampin and risperidone should be monitored for clinical efficacy of risperidone, especially with rifampin dosing changes; risperidone dosing should be adjusted accordingly. With regards to mood stabilizing medication: Consider an alternative medication to carbamazepine and diazepam; if used, monitor for clinical efficacy and adjust dosing as needed. Monitor therapy and adjust dosing as needed with valproic acid.

Levofloxacin, bedaquiline, delamanid: There are multiple interactions between levofloxacin, bedaquiline, and delamanid with medicines used for SMD due to increased risk for QT-prolongation. Patients on either amitriptyline, fluoxetine, or lithium should be monitored for QT-prolongation and arrhythmias by ECG. Avoid using haloperidol, risperidone, chlorpromazine, or clozapine if possible. If using, monitor for QT-prolongation and arrhythmias on ECG. Additionally for bedaquiline and delamanid: it is not recommended to use carbamazepine, as carbamazepine may reduce the levels and efficacy of these medications.

Linezolid: There are multiple interactions between linezolid and medicines used for SMD due to serotonergic effects, dopamine antagonism, and monoamine oxidase inhibition. Do not use with amitriptyline, fluoxetine, or lithium due to the risk of serotonin syndrome. If using with haloperidol, risperidone, chlorpromazine, fluphenazine, or clozapine, monitor clinically for signs of serotonin syndrome or neuroleptic malignant syndrome. Additionally for clozapine: Monitor neutrophil count closely. Do not use with carbamazepine due to the risk of excessive monoamine oxidase inhibition.

There are no significant interactions between **pyrazinamide, rthambutol, or cycloserine** and medicines used for SMD.

Hepatitis

[The following information is summarized from drug-drug interaction searches using Lexi-Interact.]

Daclatasvir and **ledipasvir** may increase levels of risperidone. Monitor for risperidone toxicity when starting and uptitrating daclatasvir or ledipasvir, and monitor for reduced risperidone efficacy when downtitrating and stopping ledipasvir.

Carbamazepine may reduce the levels and efficacy of multiple hepatitis medicines, including **daclatasvir**, **sofosbuvir**, and **ledipasvir**. It is not advised to combine carbamazepine with these medicines.

See Annex for further details.

Relevant WHO guidelines

Tuberculosis

Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

<http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1>

RECOMMENDATIONS ON TREATMENT OF DRUG-SUSCEPTIBLE TB*

Effectiveness of shortened fluoroquinolone-containing regimens

In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen.

Effectiveness of TB treatment using fixed-dose combination tablets

The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.

Effectiveness of intermittent dosing (thrice weekly) of TB medications

In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency

Initiation of antiretroviral treatment in TB patients living with HIV

- ✓ ART should be started in all TB patients living with HIV regardless of their CD4 cell count.
- ✓ TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm³) should receive ART within the first 2 weeks of initiating TB treatment.

Duration of TB treatment for HIV co-infected patients

In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more.

The use of adjuvant steroids in the treatment of extrapulmonary TB disease

- ✓ In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.
- ✓ In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.

The empirical use of the WHO category II regimen in patients who require retreatment for TB

In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen.

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update.

<http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1>

Note: The guidelines are currently being updated and the recommendations will be replaced with the revised ones as soon as they are available.

1. Shorter MDR-TB regimen

In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence).

2. Longer MDR-TB regimens

2a) In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C2 (conditional recommendation, very low certainty in the evidence). If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.³

2b) In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

(Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine).

(Group D2=bedaquiline, delamanid; Group D3=p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin clavulanate, (thioacetazone)).

Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

<http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1>

(Alipanah et al, 2018)

Recommendations

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (Strong recommendation, moderate certainty in the evidence)

A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option (Conditional recommendation, low certainty in the evidence)

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracers and/or digital medication monitor (Conditional recommendation, very low certainty in the evidence) b) material support to patient (Conditional recommendation, moderate certainty in the evidence) c) psychological support to patient (Conditional recommendation, low certainty in the evidence) d) staff education (Conditional recommendation, low certainty in the evidence).

[The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence).

*Psychological support includes counselling sessions and peer-group support.]

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. However, the GDG had concerns about confounding in these studies due to the severity of illness in the groups receiving support. Additionally, allocation of patients to the support groups was not always randomized. When considering this data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

Hepatitis

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015

http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

Who to treat and who not to treat in persons with chronic hepatitis B	
Who to treat	- As a priority, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. (Strong recommendation, moderate quality of evidence) - Treatment is recommended for adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status. (Strong recommendation, moderate quality of evidence) - Where HBV DNA testing is not available: Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status. (Conditional recommendation, low quality of evidence)
First-line antiviral therapies for chronic hepatitis B	
	- In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. (Strong recommendation, moderate quality of evidence) - NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are

	not recommended. (Strong recommendation, moderate quality of evidence)
Second-line antiviral therapies for the management of treatment failure	
	In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended. (Strong recommendation, low quality of evidence)
When to stop treatment	
Lifelong NA therapy	All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analogues (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (Strong recommendation, low quality of evidence)
Discontinuation	- Discontinuation of NA therapy may be considered exceptionally in: - persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults); - and who can be followed carefully long term for reactivation; - and if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and after completion of at least one additional year of treatment; - and in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (where HBV DNA testing is available). - Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. (Conditional recommendation, low quality of evidence)

Abbreviations: ALT alanine aminotransferase, anti-HBe antibody to hepatitis B e antigen, APRI aspartate aminotransferase-to-platelet ratio index, CAPD continuous ambulatory peritoneal dialysis, CHB chronic hepatitis B, HBsAg hepatitis B surface antigen, HBV hepatitis B virus, HCV hepatitis C virus

Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016
<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/>

New recommendations (2016): Treatment with direct-acting antiviral agents: it is recommended that direct-acting antivirals (DAA) regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. (Strong recommendation, moderate quality of evidence)

Subgroup considerations: for patients with HCV genotype 3 infection with cirrhosis and patients with genotypes 5 and 6 infection with and without cirrhosis, an interferon-based regimen: sofosbuvir/pegylated interferon and ribavirin is recommended as an alternative treatment option.

Preferred and alternative regimens for the treatment of persons with chronic hepatitis C virus infection based on genotype is also provided.

With regards to Interferon, WHO Hepatitis Guidelines advise the following:

- **WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (2015)**: "...IFN cannot be used in persons with decompensated cirrhosis, pregnancy, thyroid disease, those with psychiatric conditions, those receiving immunosuppressive therapy for coexisting conditions, or in infants less than 1 year of age."
- **WHO Guidelines for the screening care and treatment of persons with chronic hepatitis C infection (2016)**: "Many persons treated with interferon will develop depression; interferon-containing regimens are contraindicated in those with uncontrolled depression, psychosis or epilepsy. There are reports of suicide among persons receiving interferon therapy and therefore careful patient selection is required in persons with depression." Additionally, uncontrolled depression or psychosis are listed as absolute contra-indications.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to Decision table

	Judgement ²	EVIDENCE	Additional considerations
PROBLEM	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ✓ ○ Varies ○ Don't know	High prevalence and high mortality – see background section. In LMICs, infectious diseases contribute to a significant amount of mortality in persons with SMD. In Ethiopia, nearly half (49%) of persons with SMD in a 10-year follow-up died due to infectious disease (49%), mostly tuberculosis (Fekadu, 2015). In India, most deaths due to physical illnesses in persons with SCZ were infectious diseases, including tuberculosis (Thara, 2004).	
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know ✓	No direct research evidence was identified.	A Russian study of TB treatment in the context of comorbidity with schizophrenia reports that following 9 months, complex treatment of pulmonary tuberculosis in schizophrenics succeeded in ceasing bacterial discharge, as shown by microscopy and sputum cultures, in 94.4 and 84.5% of cases, respectively. (Mishin et al, Probl Tuberk Bolezn Legk. 2008;(6):6-10. 2008)
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ○ Large	See drug-drug interactions information above and Annex.	

² These were made based on the available evidence and/or the GDG's expertise.

	○ Moderate ○ Small ✓ ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies ✓	No research evidence was identified.	
VALUES AND PREFERENCES	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ✓	The main outcomes are infectious disease-related outcomes and frequency of adverse events/side-effects. The 2nd national survey of Australians living with psychotic illness indicated that physical health related issues are rated as more concerning to the consumer than their uncontrolled symptoms of mental illness (Morgan et al 2012).	
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the	No direct research evidence available.	

	comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know ✓		
RESOURCES REQUIRED	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ✓ ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A randomized clinical trial (n=236) compared enhanced treatment as usual (Control) to a brief intervention to deliver best practice services for blood-borne diseases in an urban, largely minority sample of dually diagnosed clients. This intervention included Screening, Testing for HIV and hepatitis, Immunization for hepatitis A and B, Risk-reduction counseling and medical treatment Referral and support (STIRR) at the site of mental health care. Clients randomized to STIRR had high levels (over 80%) of participation and acceptance of core services. They were more likely to be tested for HBV and HCV; immunized for hepatitis A and B; increase their hepatitis knowledge and to reduce their substance abuse. However, they showed no reduction in risk behavior, were no more likely to be referred to care (81 vs. 75%) and showed no increase in HIV knowledge. Intervention costs were \$541 per client (Rosenberg 2010). The patient-incurred costs illustrate that the financial burden of illness is relatively greater for patients in poorer countries without universal healthcare coverage. Systematic literature review: From the provider perspective, mean DS-TB treatment costs per patient were US\$14,659 in high-income countries (HICs), US\$840 in upper middle-income countries (UMICs), US\$273 in lower middle-income (LMICs), and US\$258 in low-income countries (LICs), showing a strong positive correlation. The respective costs for treating MDR-TB were US\$83,365, US\$5284, US\$6313 and US\$1218. Costs incurred by patients when seeking treatment for DS-TB accounted for an additional 3 % of the provider costs in HICs. A greater burden was seen in the other income	

		groups, increasing the costs of DS-TB treatment by 72 % in UMICs, 60 % in LICs and 31 % in LMICs. When provider costs, patient costs and productivity losses were combined, productivity losses accounted for 16 % in HICs, 29 % in UMICs, 40 % in LMICs and 38 % in LICs (Laurence YV, 2015).	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ✓ ○ High ○ No included studies	See above	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ✓ ○ Varies ○ No included studies	• Short course drug treatment for new smear-positive cases of TB has been promoted as one of the most cost effective healthcare interventions available, based on a study covering countries with some of the highest rates of tuberculosis infection in sub-Saharan Africa and South East Asia with the cost per DALY averted at around < US\$2 in both regions (Baltussen et al, 2005). • Treatment for multidrug-resistant tuberculosis (MDR-TB) can be cost effective in low- and middle-income countries (Fitzpatrick 2012).	
EQUITY	What would be the impact on health equity? ○ Reduced	• People with SMD have a higher prevalence of infectious disease as compared to the general population; the interventions would improve equity in health as they would address both the heightened risk of these diseases as well as the premature mortality when co-morbidity exists.	

	○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ✓ ○ Varies ○ Don't know	The WHO End TB strategy calls to provide TB care through an integrated approach in collaboration with other public health programmes including mental health services such as tailoring TB care delivery models to the specific needs of populations with mental health problems. • Some clinical practices have excluded populations with mental health and/or substance use problems from accessing interferon therapy because they were considered as having contraindications to treatment, particularly due to the neuropsychiatric effects of interferon that can occur in some patients. (Hepworth 2013).	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ✓ ○ Varies ○ Don't know	• In the general population, individuals with TB and their health-care providers identify TB stigma as a cause of non-completion of anti-TB treatment. Even after the start of therapy, concern about being identified as having TB and suffering the consequences of TB stigma may lead individuals to drop out of treatment programs. TB stigma has also been raised as a potential barrier to home- and work-based patient-centred direct observational therapy (DOT), given that the presence of TB nurses might mark a person as infected. Quantitative studies have yielded mixed results (Edginton 2002, Naidoo 2009, Ngamvithayapong 2001).	Counselling and support increases participation and acceptance of services (see STIRR trial above)
FEASIBILITY	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ✓ ○ Varies ○ Don't know	Most of the medicines are available in the WHO essential medicine list.	

Relevant parts from WHO guidelines

See section on WHO guidelines above.

GDG Recommendations

For people with severe mental disorder (SMD) and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological interventions are effective for treatment of infectious diseases (e.g. tuberculosis, hepatitis B, hepatitis C)?

TYPE OF RECOMMENDATION	Strong recommendation against the option ○	Conditional recommendation against the option ○	Conditional recommendation for either the option or the comparison ○	Conditional recommendation for the option ○	Strong recommendation for the option ○ ✓
RECOMMENDATION	Recommendations Recommendation 1: For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the <i>WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care</i>, and the <i>WHO treatment guidelines for drug-resistant tuberculosis</i>. (<i>Strength of the recommendation: strong; Quality of the evidence: Low</i>). Recommendation 2: For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the <i>WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care</i>, and the <i>WHO treatment guidelines for drug-resistant tuberculosis</i> (<i>Strength of the recommendation: strong; Quality of the evidence: Low</i>). Recommendation 3: For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the <i>WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection</i>. (<i>Strength of the recommendation: strong; Quality of the evidence: Low</i>) Recommendation 4: For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the <i>WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection</i>. (<i>Strength of the recommendation: strong; Quality of the evidence: Low</i>) Best practice for people with severe mental disorders and TB, Hepatitis B/C: ○ Prescribers should take into account the potential for drug-drug interactions between TB				

	medicines, medicines for hepatitis B and C with psychotropic medicines. <u>Additional consideration:</u> • People with SMD may be at an increased risk of Hepatitis B and C for example due to injection drug use. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA (https://www.cdc.gov/hepatitis/populations/idu.htm).
JUSTIFICATION	No reviews were identified for interventions in people with SMD and comorbid TB, Hepatitis B/C. A recent systematic review reported that programmes that included educational, psychological, and/or material support were associated with better TB outcomes, and can now be considered best practice (Alipanah et al., 2018). Some trial evidence shows effectiveness of treatment of pulmonary tuberculosis in people with SMD (Mishin et al 2008) and of a brief intervention to deliver best practice services for infectious diseases to people with mental disorders in increasing participation and acceptance of core services, including testing for hepatitis B/C; immunization for hepatitis A and B; increased hepatitis knowledge reduction of substance use (Rosenberg 2010). The drug-drug interaction review showed that major interactions exist between medicines used for TB, hepatitis B/C and psychotropic medicines (Annex 6). These require close clinical monitoring and dose adjustments and in some cases use of alternate psychotropic medicines with less potential for interaction. These recommendations are based on indirect evidence of TB/Hepatitis treatment in the general population that are provided in existing WHO guidelines as the GDG concluded that the same pathophysiological mechanisms for these conditions would apply to people with SMD. The GDG provided strong recommendations as they agreed that the benefits of the interventions outweighed the harms while noting the need to consider drug interactions. The GDG also agreed that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. GDG also agreed that people with SMD would need additional support for adherence and provided a strong recommendation for this.

SUBGROUP CONSIDERATIONS	People with SMD may be at an increased risk of Hepatitis B and C for example due to injection drug use. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with severe mental disorders who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA (https://www.cdc.gov/hepatitis/populations/idu.htm).
IMPLEMENTATION CONSIDERATIONS	Follow WHO TB guidelines for non pharmacological (social, psychological) interventions (see above)
MONITORING AND EVALUATION	It will be good to include mental health in TB reporting and recording systems in order to understand the scale of the problem
RESEARCH PRIORITIES	• RCTs are required to test the efficacy of the different types of non-pharmacological interventions that exclusively target people with SMD and infectious diseases TB, Hepatitis B/C). • Research is needed on integrated care models that include treatment of SMD and TB, Hepatitis B/C to improve both health and mental health outcomes.

Remarks

- No reviews were identified for interventions in people with SMD and comorbid TB, Hepatitis B/C.
A recent systematic review reported that programs that included educational, psychological, and/or material support were associated with better TB outcomes, and can now be considered best practice (Alipanah N et al. 2018)

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2. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update.
<http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1>
3. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015
http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1
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**PRISMA Flow Diagram for systematic review of the reviews:
SMD and 'other infectious diseases' (Tuberculosis, Hepatitis B/C)**

