Drug use disorder module - evidence profile DRU2: Pharmacotherapies for adults with cocaine or stimulant dependence

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

2023

World Health Organization

Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1. Background

Stimulant dependence, comprising cocaine-type and amphetamine-type stimulant dependence is increasing in prevalence[1] and contributes to substantial burden worldwide[2]. Regions particularly affected by it include East and Southwest Asia, for methamphetamine, and North and Tropical Latin America, for cocaine[3]. Use of stimulants is related to several adverse outcomes, such as psychosis, heart disease, cognitive impairment, and overdose[4,5]. It is also associated with infectious diseases, such as hepatitis C and HIV[6] as well as legal and social consequences[7]. Overdose death rates from stimulants are increasing with and without the presence of opioids in the USA, in what is called the fourth wave of the opioid crisis[8].

Most of the evidence-based treatment modalities for cocaine and amphetamine-type stimulant dependence are non-pharmacological, including psychosocial interventions such as Contingency Management[9] and Cognitive-Behavioural Therapy[10,11], as well as repetitive transcranial magnetic stimulation and exercise[12]. To date, there are no medicines approved by the regulatory agencies for the use in treatment of stimulant dependence. However, a large number of medicines have been tested in controlled trials. While antidepressants[13,14] and antipsychotics[15] have not demonstrated efficacy with a sufficient number of clinical trials, systematic reviews on other medicines offer evidence that may be used to support pharmacotherapy for cocaine and amphetamine dependence.

Prescription psychostimulants are deemed as a potentially effective and safe medicine to treat stimulant dependence, with more recent trials supporting their use in extended-release formulations and higher dosages[16]. Other medicines, such as bupropion[17,18], naltrexone[19], and topiramate[20], have shown some efficacy in drug-related outcomes such as sustained abstinence and reduction in drug use. More recently, mirtazapine has been tested among sexual and gender minority subgroups showing promise to reduce methamphetamine use among those populations[21]. Combinations among those medicines, such as prescription amphetamines and topiramate for cocaine dependence[22,23] and bupropion and naltrexone for methamphetamine dependence[24] are also potential alternatives for clinical practice.

This report aims to review and grade the existing evidence to answer some of the outstanding questions and provide guidance to providers. It uses a structured approach to evidence review as outlined in WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714.

Considering that several high-quality reviews have been published recently we will provide a new review of the reviews in order to reassess if the recommendation remain the same as outlined in the latest mhGAP guide. We will focus on several medicines that have been recently evaluated including: naltrexone, dexamphetamine, methylphenidate, modafinil, topiramate, mirtazapine, and bupropion.

Below are outlined the methods that were used in preparation of the report together with details of the results and a discussion with recommendations.

2. Methodology

2.1. PICO question

Are medicines safe and effective to treat cocaine or stimulant dependence?
Population (P): Adults with cocaine or stimulant (amphetamines, methamphetamines) dependence
Intervention (I): pharmacotherapy with naltrexone, dexamphetamine, methylphenidate, modafinil, topiramate, mirtazapine, bupropion
Comparator (C): placebo or treatment as usual
Outcomes (O):

List critical outcomes:

- **Critical outcome 1:** drug consumption
- **Critical outcome 2:** drug abstinence (sustained)
- **Critical outcome 3:** harm from drug use
- Critical outcome 4: retention to treatment

List important outcomes:

- **Important outcome 1:** Adverse effects
- **Important outcome 2:** Improvements in other areas of health and functioning

Subgroups: cocaine, amphetamine-type stimulants

2.2. Search strategy

The search was conducted in March 2022, using the following databases: PubMed/MEDLINE, PsychInfo, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus, Open Science Framework (OSF), and Cochrane.

The selection criteria that were applied to search terms was based on:

- Type of studies - **systematic reviews only**
- Types of participants - **adults 18 to 65 years old, though we included reviews with slightly different inclusion criteria.**
- Types of interventions - **medicines to treat cocaine or other stimulant dependence - prescription amphetamines, methylphenidate, modafinil, bupropion, topiramate, naltrexone, mirtazapine**
- Types of outcome measures -
  Critical outcomes: drug consumption, drug abstinence (sustained), harm from drug use, retention to treatment;
  Important outcomes: adverse effects, improvements in functioning
- Published language of study - **any language**
- Date range - **2018 - 2022**

The following search strategies were used for cocaine and amphetamines/methamphetamine, respectively:

"systematic review" and cocaine and [medication name]

"systematic review" and (amphetamine* or methamphetamine*) and [medication name]

Medication name was defined as "(dexamphetamine or dextroamphetamine or "mixed amphetamine salts" or lisdexamphetamine)" for prescription amphetamines; "methylphenidate", "modafinil", "bupropion", "topiramate", "naltrexone", "mirtazapine" were used as simple terms.

2.3. Data collection and analysis

As the first stage of article selection, records were retrieved from the bibliographic databases. Next, they were assessed for eligibility by title and then abstract, according to the inclusion and exclusion criteria described before. The articles considered relevant at this stage were moved on to full-text screening and the same criteria were applied. Data from the eligible studies were then extracted following a template defined a priori that includes author name, study design, population characteristics, medications included, comparator, and outcomes. A team of two researchers was responsible for independently assessing the eligibility of the studies included in the full-text screening phase and extracting data from them. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to ensure transparency of the titles included and excluded in each phase until the final cohort is defined. Reasons for exclusions were provided. The final results were discussed and reviewed by all five members of the research team.

2.4. Selection and coding of identified records

All the reviews were added to an Endnote X9 [25] library. The included reviews from different databases were included in different sections within the library. The references are provided in this document.

2.5. Quality assessment

Quality of the included systematic reviews was assessed using the AMSTAR quality appraisal tool. Moreover, the quality of evidence for each outcome was assessed using the GradePro software.

2.6. Analysis of subgroups or subsets

The included articles will be divided into drug of abuse (cocaine and methamphetamine) and treatment drug (Topiramate, Naltrexone, Mirtazapine Methylphenidate, Modafinil, Prescription Amphetamines, and Bupropion). Other subgroup analyses will be reported if available on the included reviews.

3. Results

3.1. Systematic reviews and/or studies identified by the search process

Table 1a. Articles identified after the search

Cocaine	
Topiramate	Nourredine 2021[26], Chan 2020[27], Buchholz 2019[28], Chan 2019[29]
Naltrexone	Chan 2019, Buchholz 2019
Mirtazapine	Chan 2019, Buchholz 2019
Methylphenidate	Fluyau 2021[30], Chan 2020, Tardelli 2020[16], Chan 2019
Modafinil	Tardelli 2020, Buchholz 2019, Chan 2019
Prescription Amphetamines	Chan 2020, Chan 2019, Tardelli 2020, Buchholz 2019
Bupropion	Chan 2020, Chan 2019, Buchholz 2019

Table 1b. Articles identified after the search

Methamphetamine	
Topiramate	Nourredine 2021, Siefried 2020[19]
Naltrexone	Chan 2020, Siefried 2020, Chan 2019a[31], Lam 2019[32]
Mirtazapine	Naji 2022[21], Siefried 2020
Methylphenidate	Fluyau 2021, Tardelli 2020, Siefried 2020, Chan 2019a
Modafinil	Tardelli 2020, Siefried 2020
Prescription Amphetamines	Siefried 2020
Bupropion	Siefried 2020

Cocaine Flowcharts

Fig. 1. Systematic reviews assessing Topiramate for the treatment of cocaine dependence

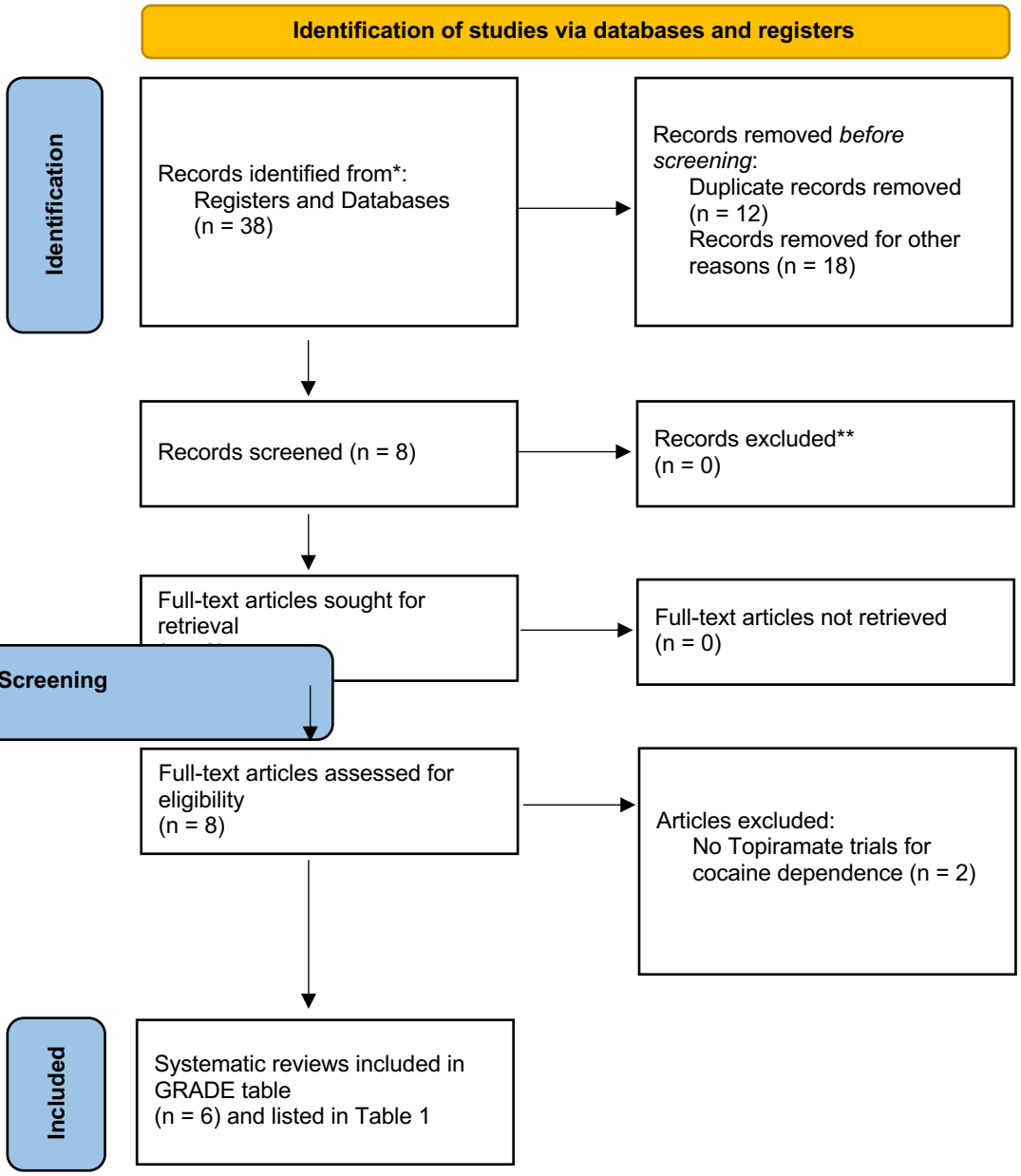


Fig. 2. Systematic reviews assessing Naltrexone for the treatment of cocaine dependence

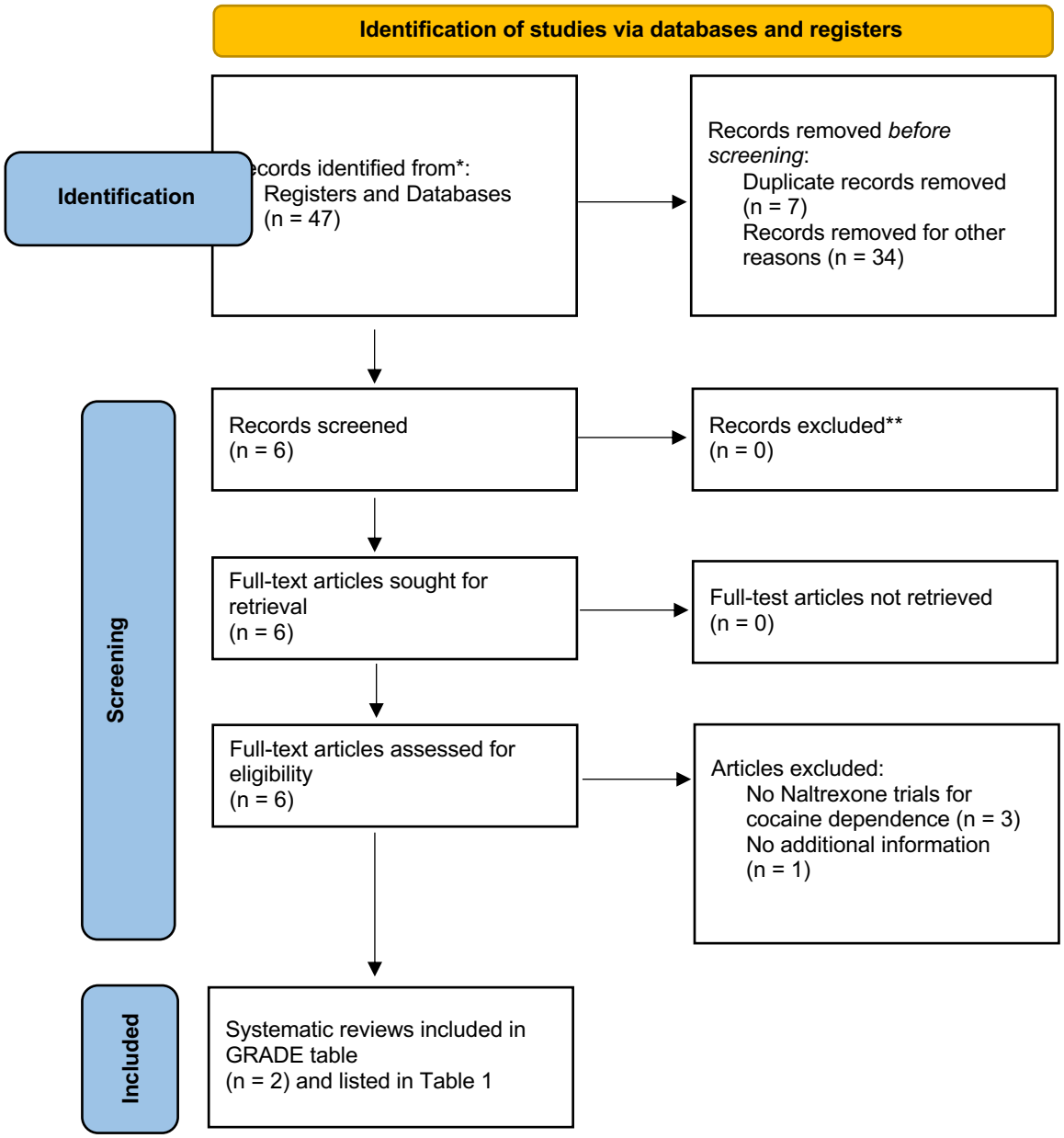


Fig. 3. Systematic reviews assessing Mirtazapine for the treatment of cocaine dependence

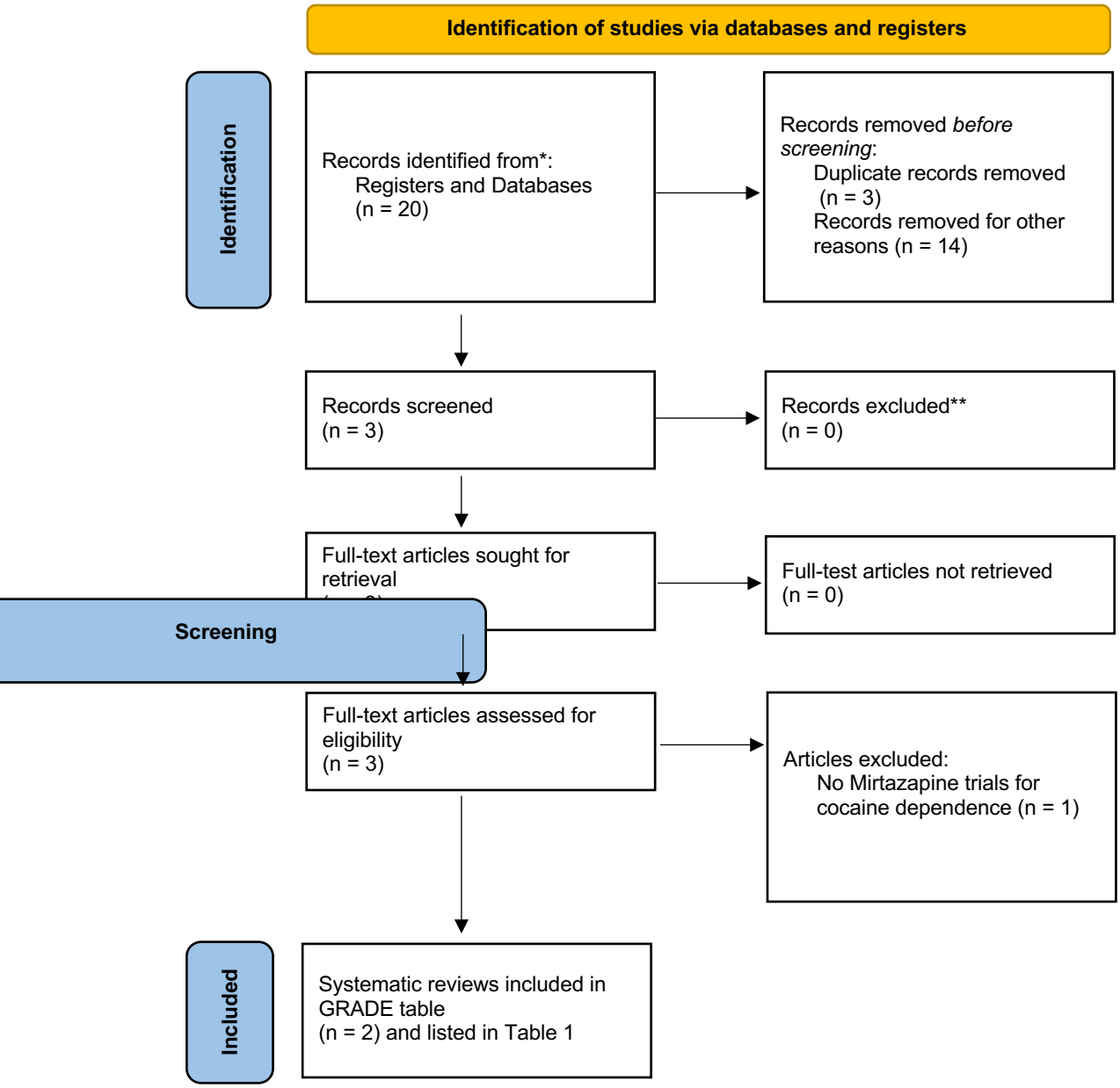


Fig. 4. Systematic reviews assessing Methylphenidate for the treatment of cocaine dependence

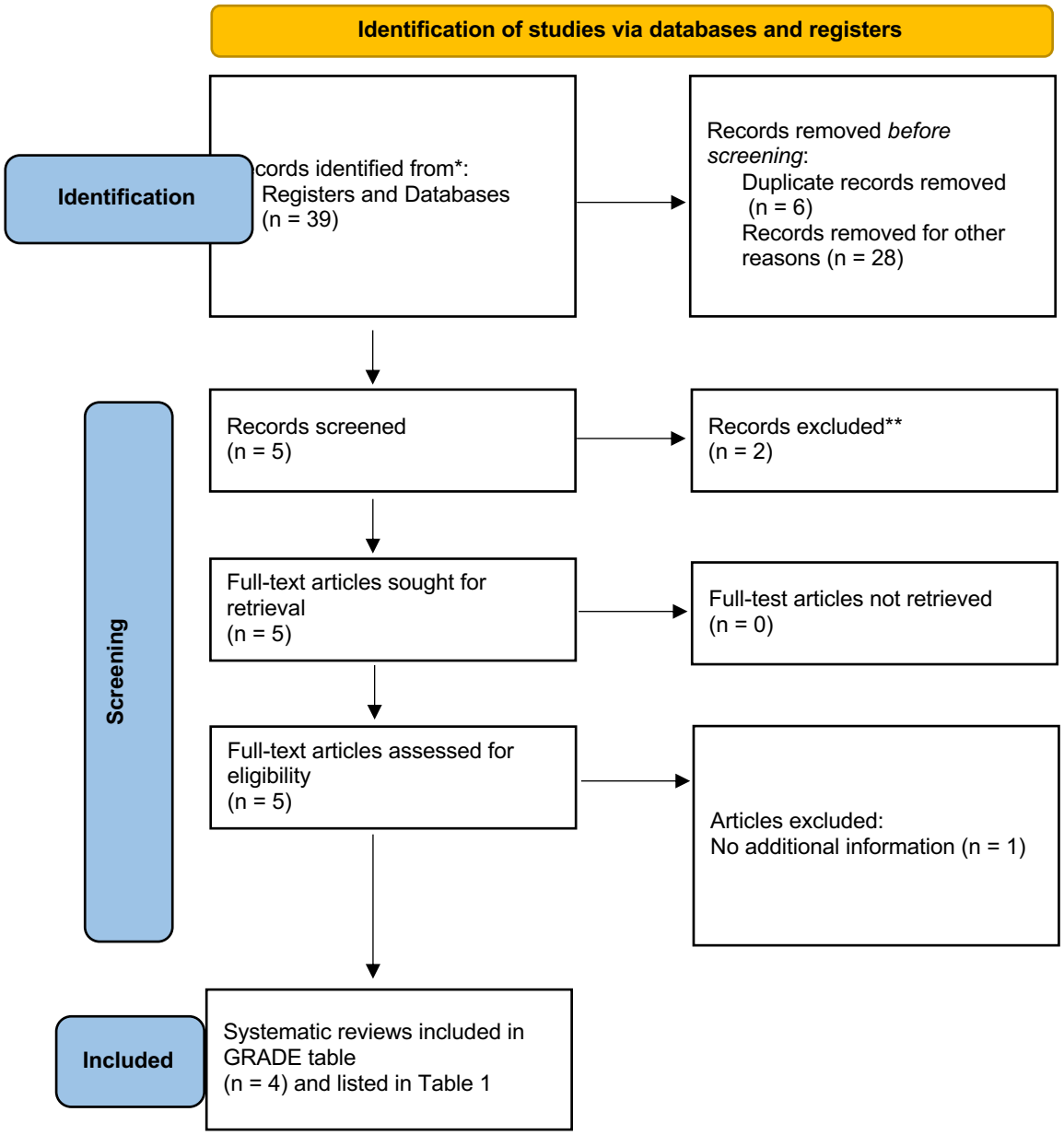


Fig. 5. Systematic reviews assessing Modafinil for the treatment of cocaine dependence

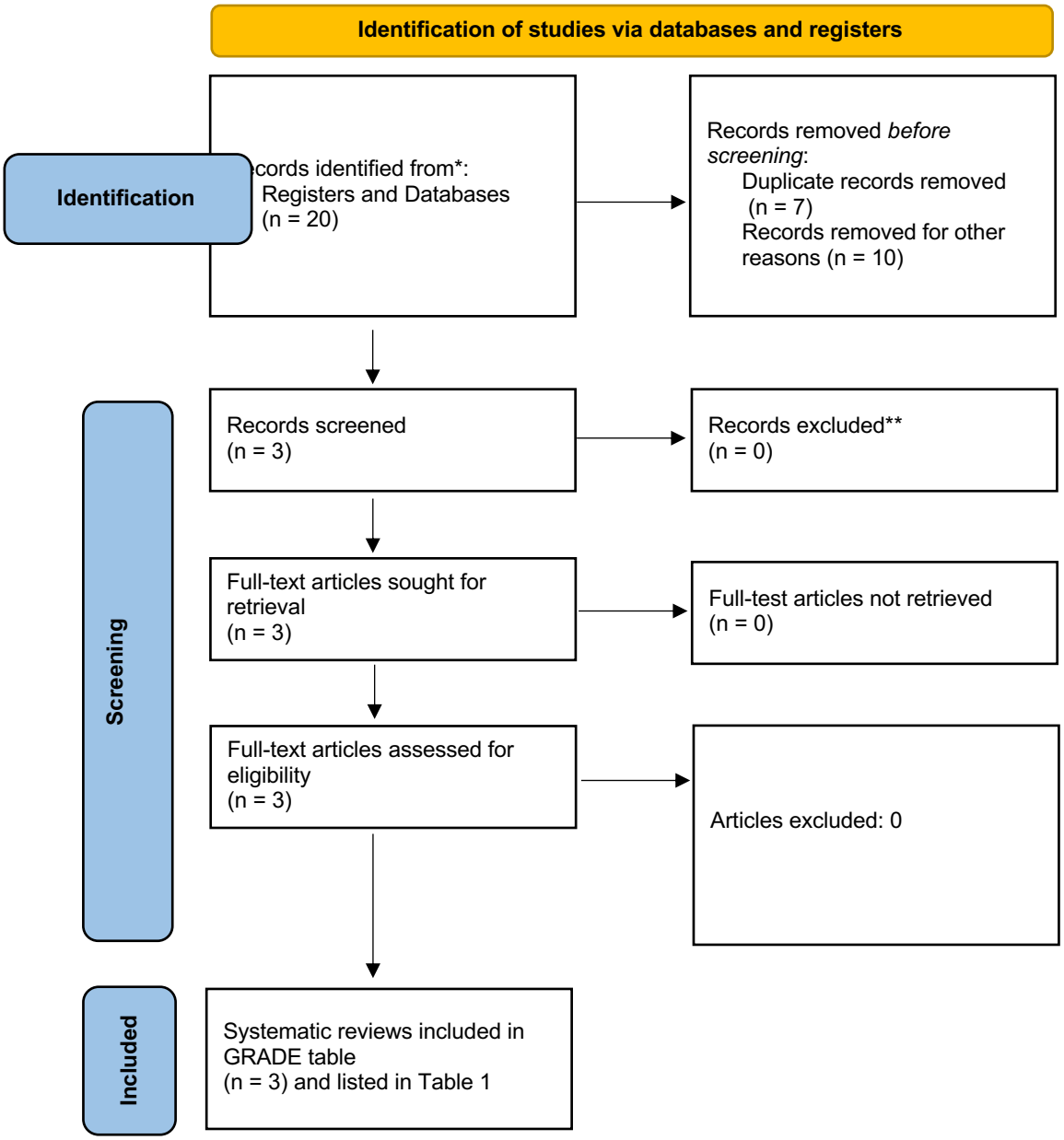


Fig. 6. Systematic reviews assessing Prescription Amphetamines for the treatment of cocaine dependence

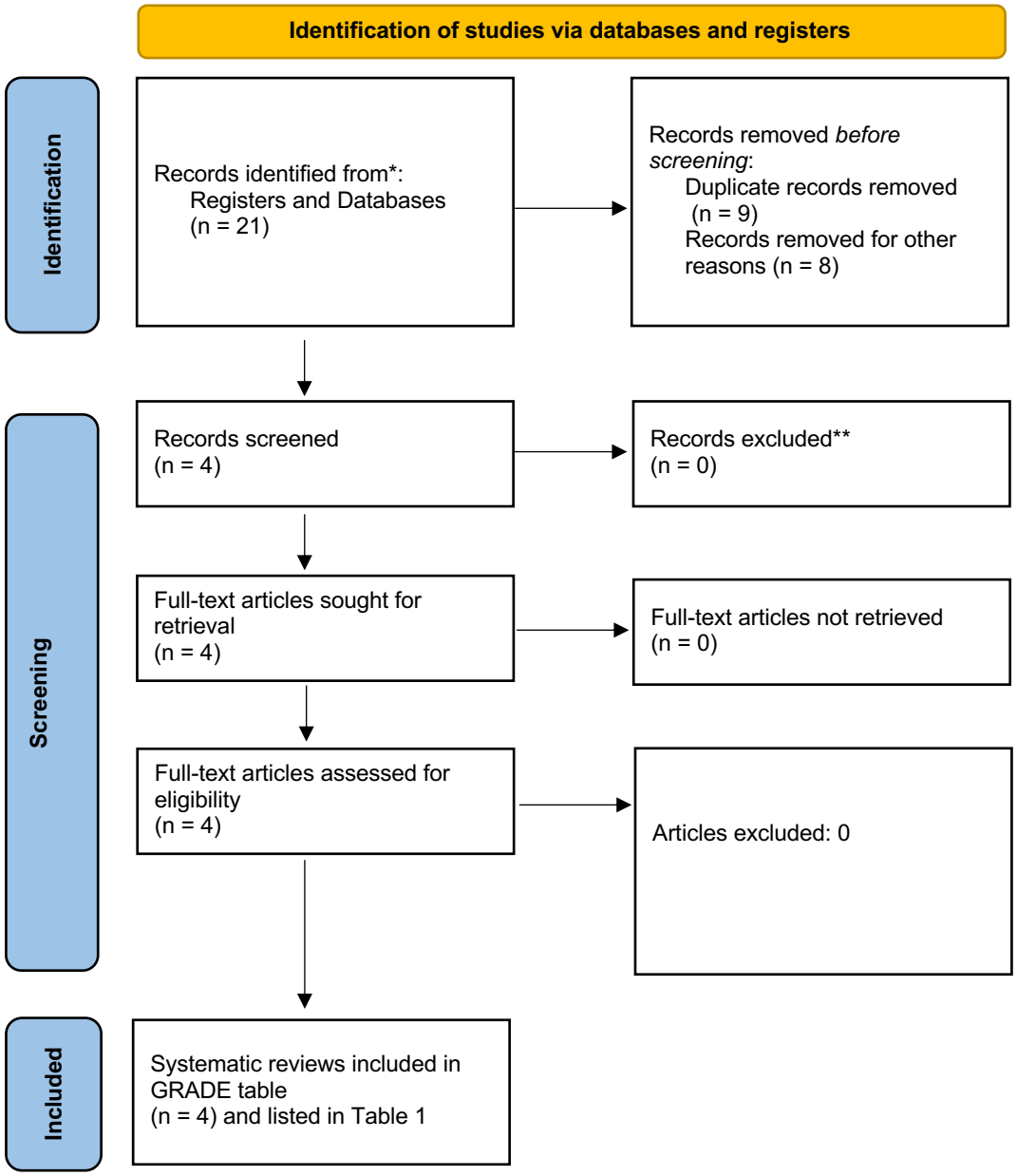
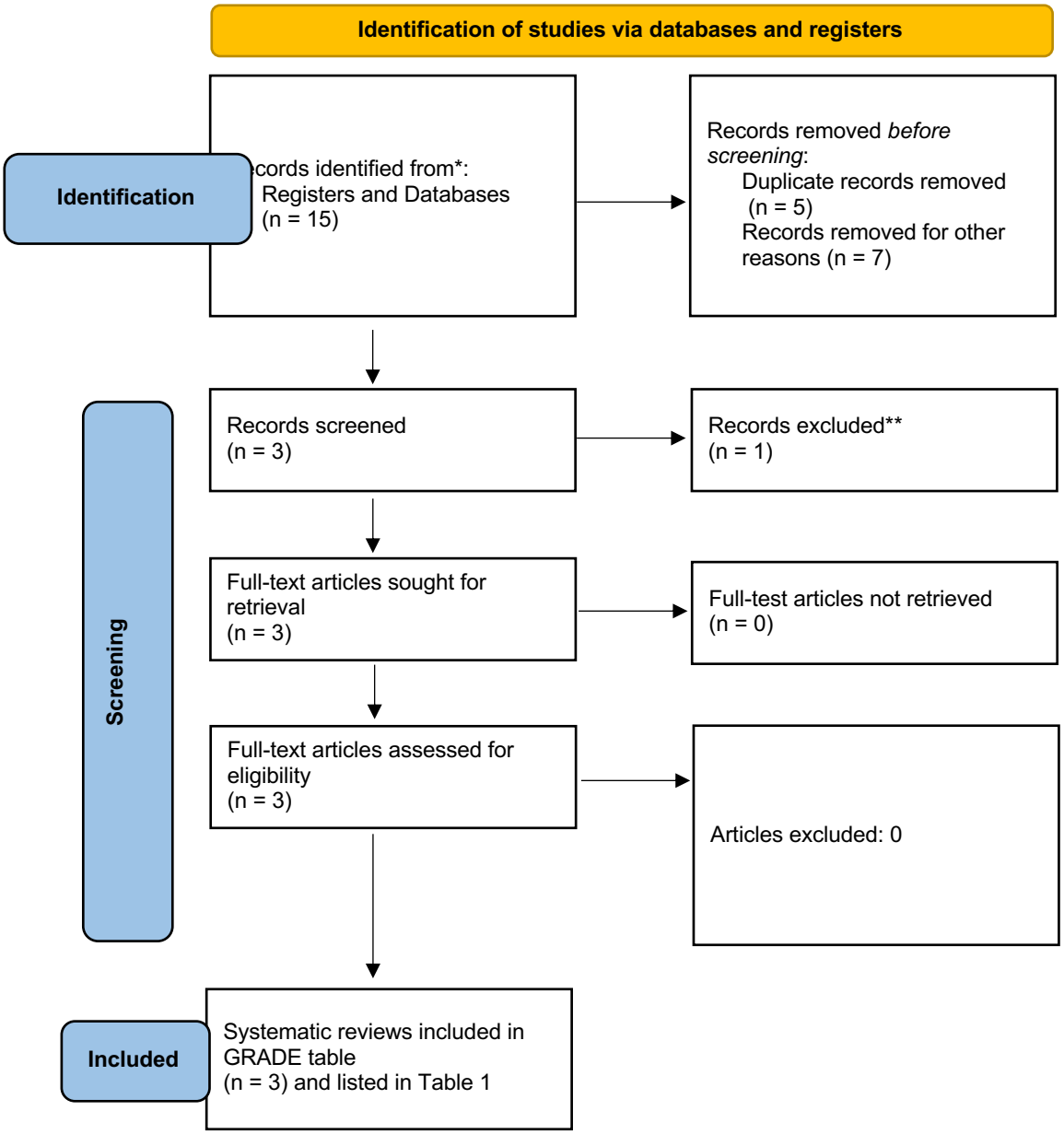


Fig. 7. Systematic reviews assessing Bupropion for the treatment of cocaine dependence



Methamphetamine Flowcharts:

Fig. 8. Systematic reviews assessing Topiramate for the treatment of methamphetamine dependence

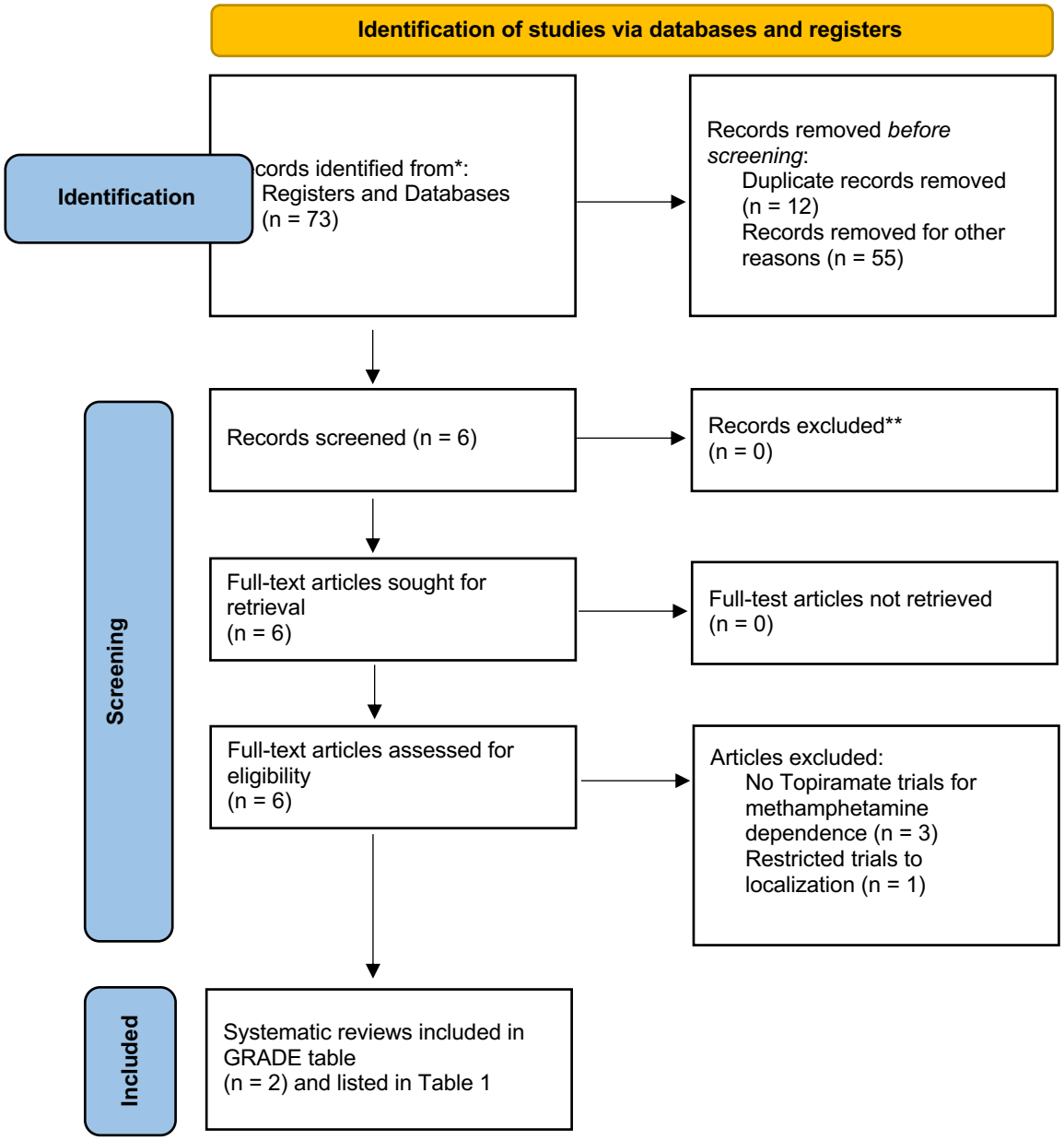


Fig. 9. Systematic reviews assessing Naltrexone for the treatment of methamphetamine dependence

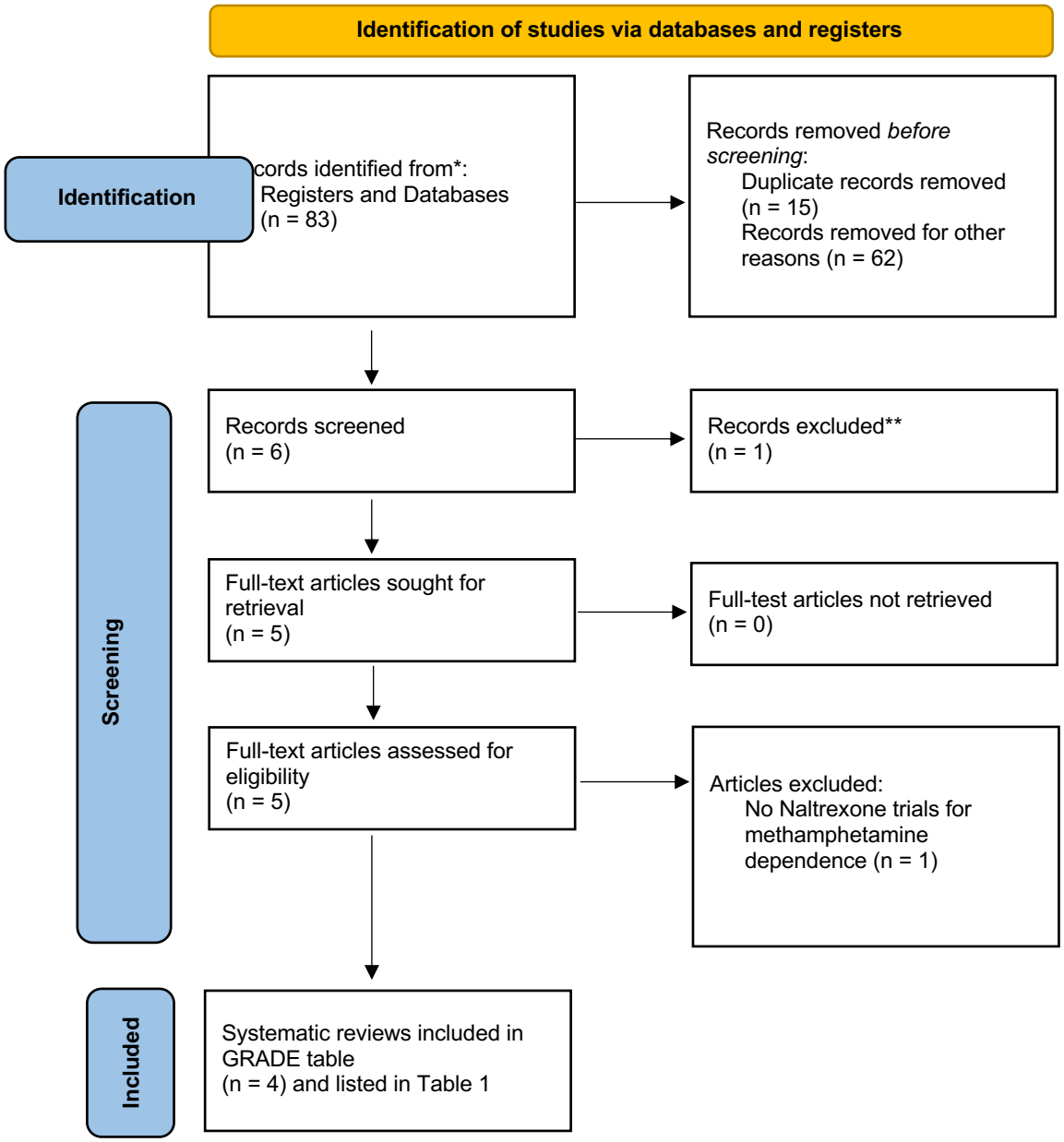


Fig. 10. Systematic reviews assessing Mirtazapine for the treatment of methamphetamine dependence

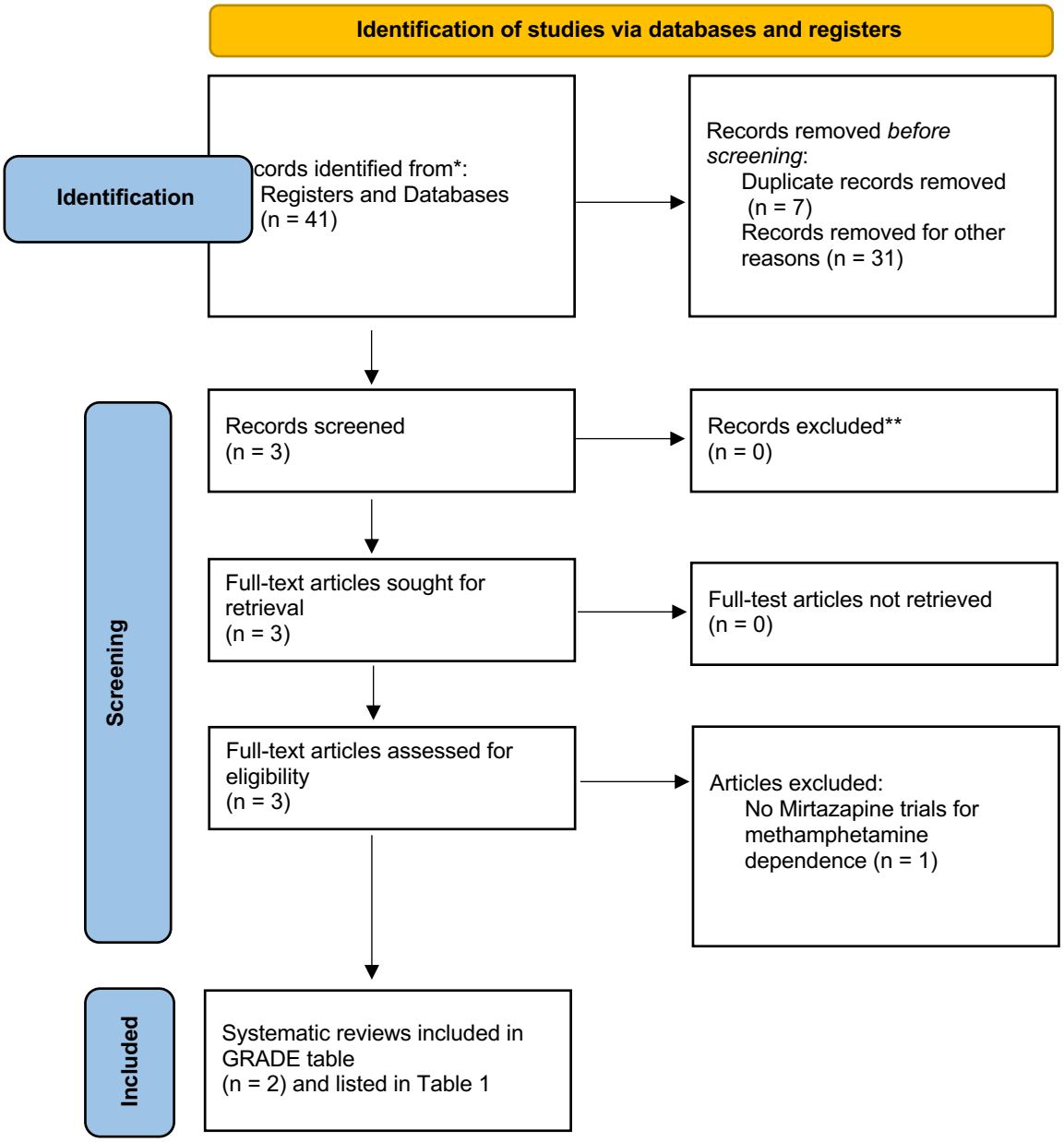


Fig. 11. Systematic reviews assessing Methylphenidate for the treatment of methamphetamine dependence

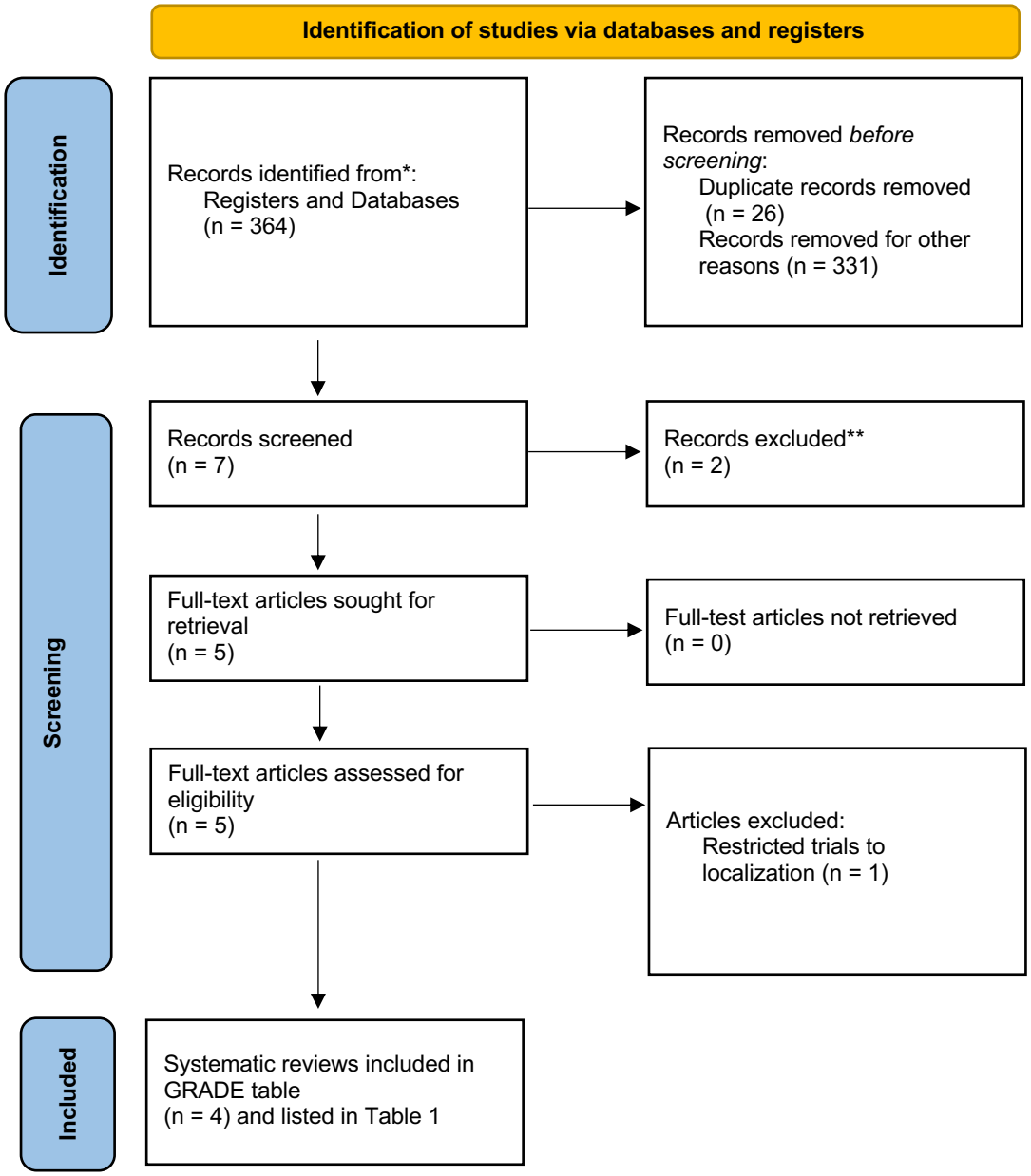


Fig. 12. Systematic reviews assessing Modafinil for the treatment of methamphetamine dependence

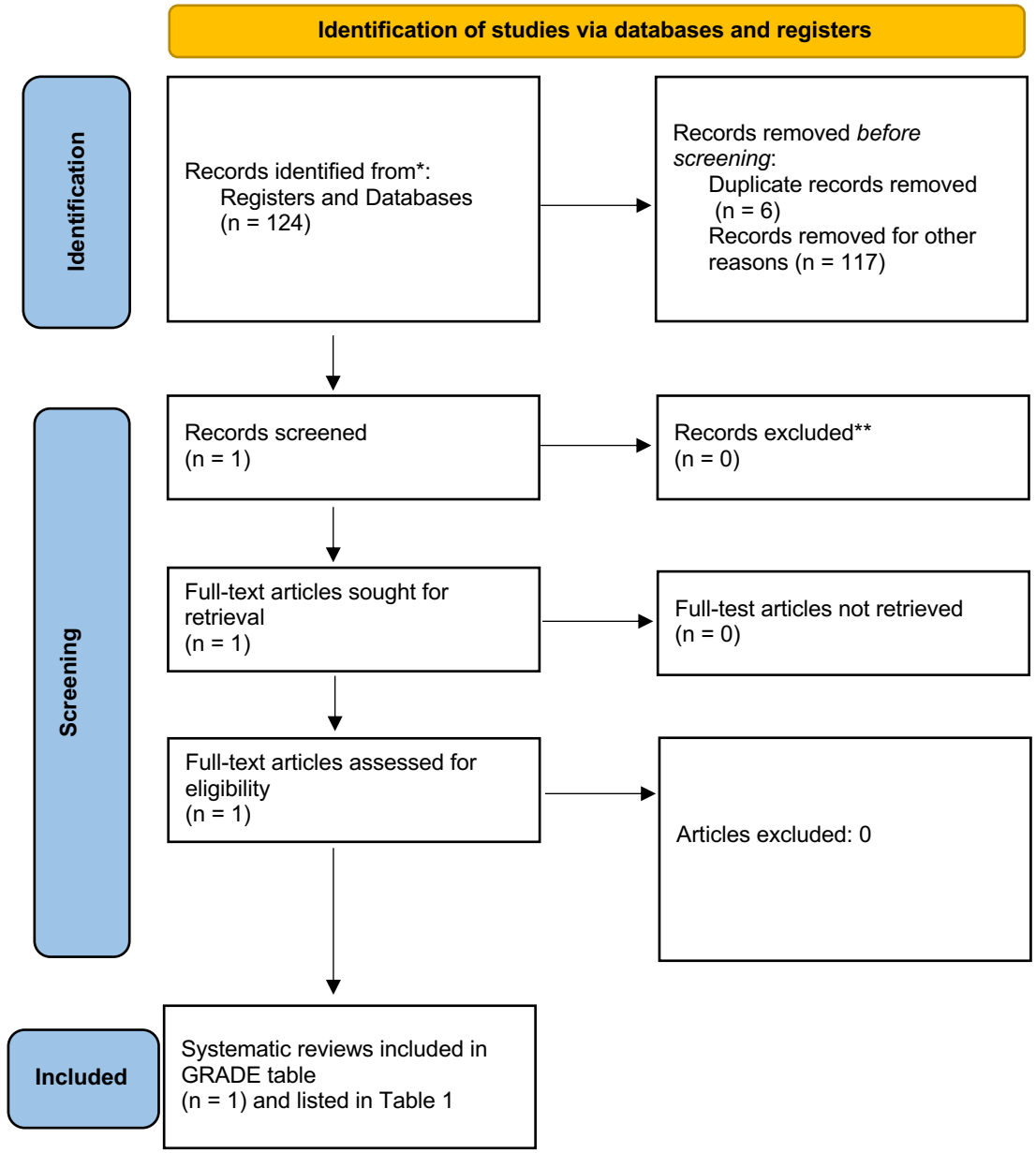


Fig. 13. Systematic reviews assessing Prescription Amphetamines for the treatment of methamphetamine dependence

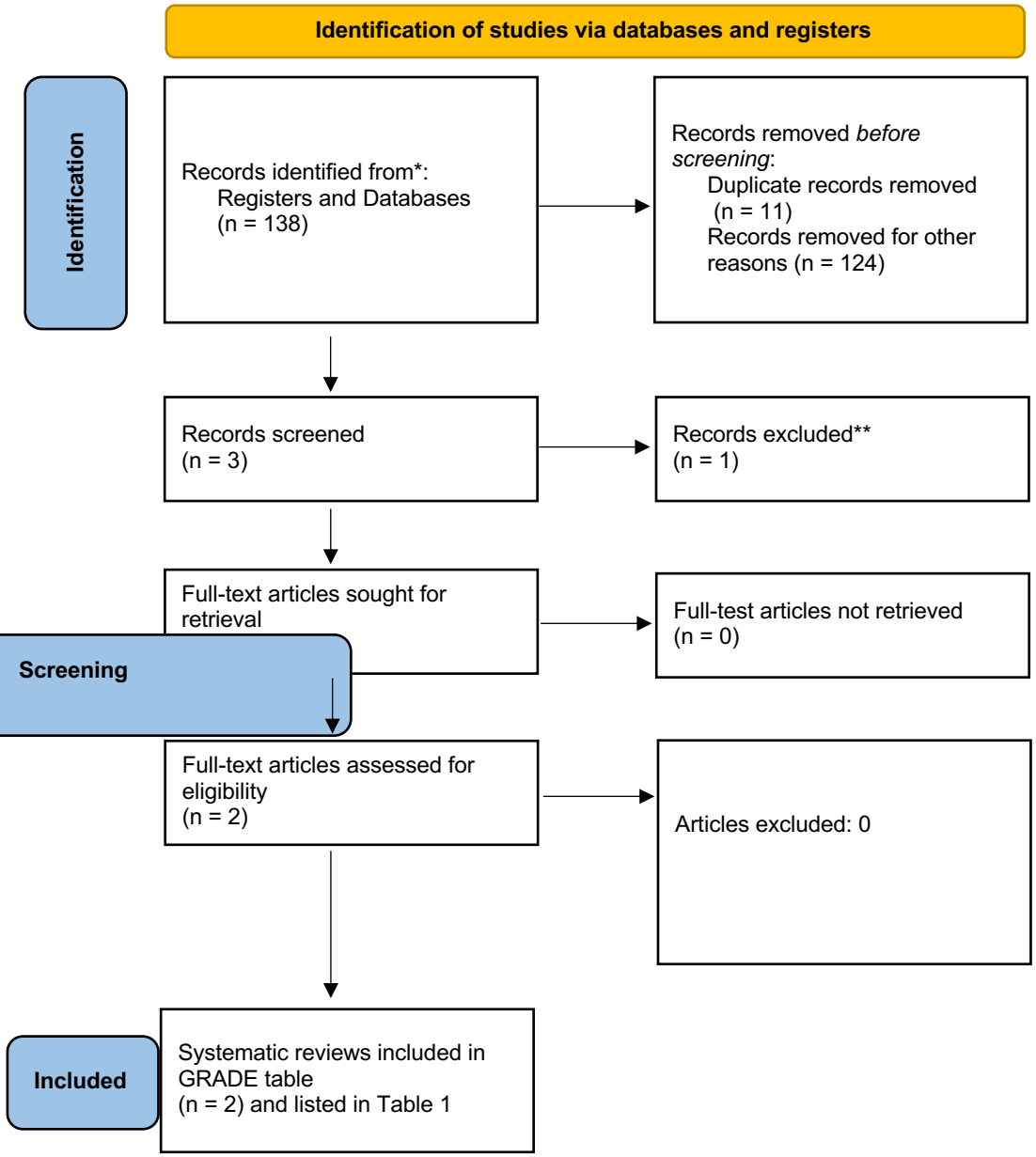
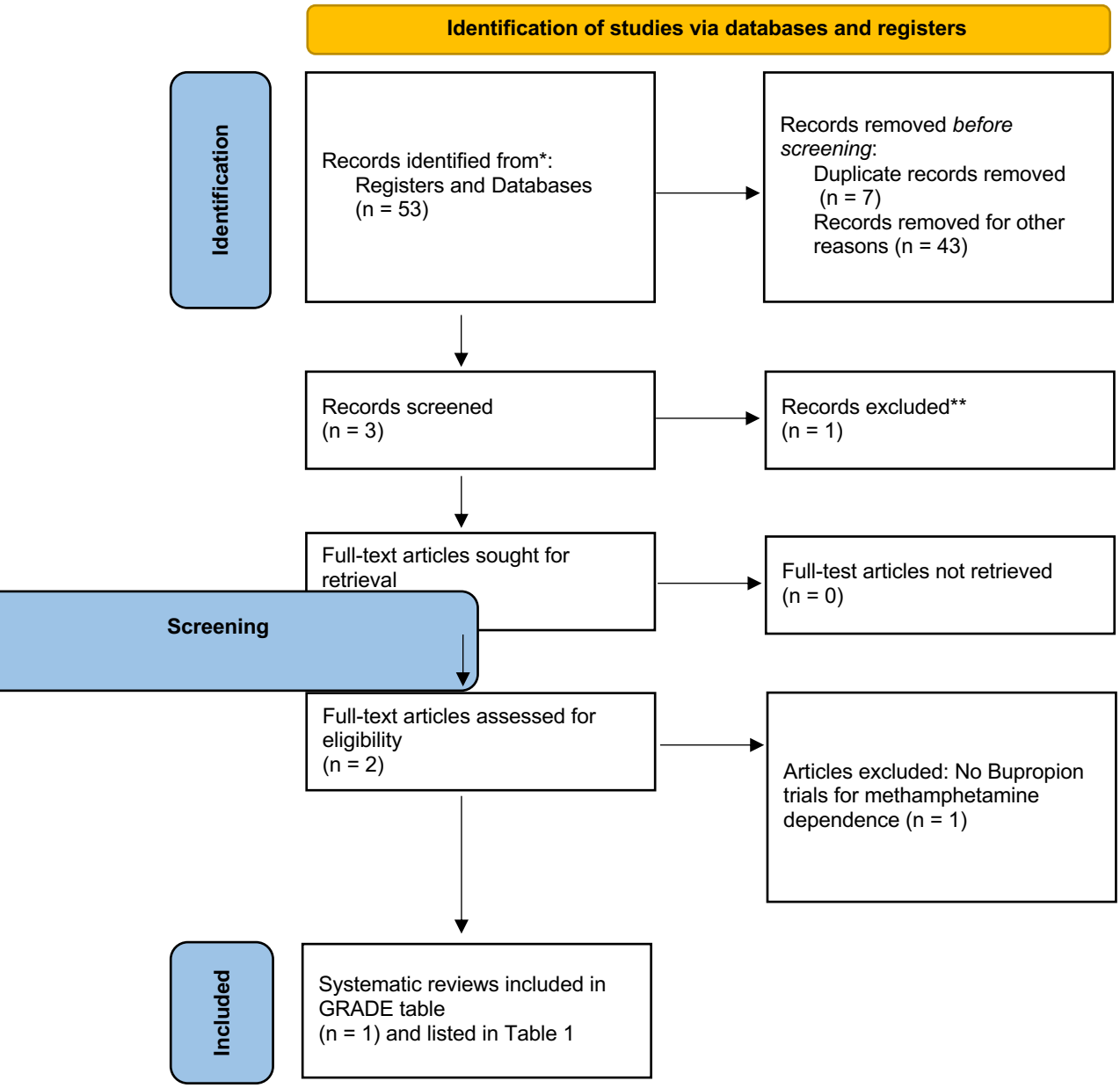


Fig. 14. Systematic reviews assessing Bupropion for the treatment of methamphetamine dependence


Identification of studies via databases and registers
Identification
Records identified from*:
Registers and Databases
(n = 53)
Records removed *before screening*:
Duplicate records removed
(n = 7)
Records removed for other reasons (n = 43)
Records screened
(n = 3)
Records excluded**
(n = 1)
Full-text articles sought for retrieval
Full-test articles not retrieved
(n = 0)
Screening
Full-text articles assessed for eligibility
(n = 2)
Articles excluded: No Bupropion trials for methamphetamine dependence (n = 1)
Included
Systematic reviews included in GRADE table
(n = 1) and listed in Table 1

3.2. List of studies included and excluded

3.2.1. Included in GRADE tables/footnotes

Table 2. Studies included in GRADE tables/footnotes
Cocaine

Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
Topiramate versus placebo	Cocaine abstinence; retention in treatment	Nourredine 2021, Chan 2020, Buchholz 2019, Chan 2019	To examine benefits of Topiramate for individuals with cocaine use disorder.
Naltrexone versus placebo	Cocaine abstinence; retention in treatment	Chan 2019, Buchholz 2019	To examine benefits of Naltrexone for individuals with cocaine use disorder.
Mirtazapine versus placebo	Cocaine abstinence; retention in treatment	Chan 2019, Buchholz 2019	To examine benefits of Mirtazapine for individuals with cocaine use disorder.
Methylphenidate versus placebo	Cocaine abstinence; retention in treatment	Fluyau 2021, Chan 2020, Tardelli 2020, Chan 2019	To examine benefits of Methylphenidate for individuals with cocaine use disorder.
Modafinil versus placebo	Cocaine abstinence; retention in treatment	Tardelli 2020, Buchholz 2019, Chan 2019	To examine benefits of Modafinil for individuals with cocaine use disorder.
Prescription Amphetamines versus placebo	Cocaine abstinence; retention in treatment	Chan 2020, Chan 2019, Tardelli 2020, Buchholz 2019	To examine benefits of Prescription Amphetamines for individuals with cocaine use disorder.
Topiramate versus placebo	Cocaine abstinence; retention in treatment	Nourredine 2021, Chan 2020, Buchholz 2019, Chan 2019	To examine benefits of Topiramate for individuals with cocaine use disorder.

Methamphetamine

Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
Topiramate versus placebo	Meth abstinence; retention in treatment	Nourredine 2021, Siefried 2020	To examine benefits of Topiramate for individuals with methamphetamine use disorder.
Naltrexone versus placebo	Meth abstinence; retention in treatment	Chan 2020, Siefried 2020, Chan 2019a, Lam 2019	To examine benefits of Naltrexone for individuals with methamphetamine use disorder.
Mirtazapine versus placebo	Meth abstinence; retention in treatment	Naji 2022, Siefried 2020	To examine benefits of Mirtazapine for individuals with methamphetamine use disorder.
Methylphenidate versus placebo	Meth abstinence; retention in treatment	Fluyau 2021, Tardelli 2020, Siefried 2020, Chan 2019a	To examine benefits of Methylphenidate for individuals with methamphetamine use disorder.
Modafinil versus placebo	Meth abstinence; retention in treatment	Tardelli 2020, Siefried 2020	To examine benefits of Modafinil for individuals with methamphetamine use disorder.
Prescription Amphetamines versus placebo	Meth abstinence; retention in treatment	Siefried 2020	To examine benefits of Prescription Amphetamines for individuals with methamphetamine use disorder.
Bupropion versus placebo	Meth abstinence; retention in treatment	Siefried 2020	To examine benefits of Bupropion for individuals with methamphetamine use disorder.

3.2.1. Excluded from GRADE tables/footnotes

None

3.3. Narrative description of studies that contributed to GRADE analysis

The systematic reviews included in the GRADE analysis were divided into two categories, according to drug of abuse: cocaine and methamphetamine reviews. Furthermore, they were divided between seven groups, according to treatment drug: topiramate, naltrexone, mirtazapine, methylphenidate, modafinil, prescription amphetamines, and bupropion, leaving the analysis with 14 subgroups. This review focused on the two most commonly reported outcomes, both with clinical relevance: abstinence (reported as a period of abstinence within the trial follow-up, usually three weeks) and retention to treatment (measured as the proportion of completers among all the individuals enrolled in the study). Other outcomes were assessed on GRADE when available.

Some of the included reviews were conducted on both cocaine and methamphetamine, and many comprised different treatment drugs. Seven reviews were included in the cocaine group[16,26-30] and eight in the methamphetamine group[16,19,21,26,27,30-32]. The reviews by Tardelli and colleagues (2020), Chan and colleagues (2020), Nourredine and colleagues (2021), and Fluyau and colleagues (2021) included both cocaine and methamphetamine. Other studies, such as Chan and colleagues (2019), Naji and colleagues (2022), and Fluyau (2021) were conducted in specific drug subgroups. The findings are heterogeneous (even within reviews of a same drug) and effect sizes are, in general, modest. Some of the reviews recommend prescription psychostimulants should be further studied. Other recommend topiramate as a potentially useful off-label therapy, though also with modest effect sizes.

3.4. Grading the Evidence

3.4.1. Cocaine reviews

Table 3a. Topiramate

Author(s): Nourredine 2021
Question: Topiramate compared to CBT or placebo for Cocaine Use Disorders
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cumulative Abstinence									
3	randomized trials	not serious	serious[a]	not serious	serious[b]	none	Topiramate did not increase abstinence rates in a meta-analysis based on two studies. Singh et al. showed that topiramate-treated patients have better odds of achieving a 3-week cocaine-free period - post hoc analysis.	⨁⨁◯◯ Low	CRITICAL
Percentage of Abstinence Periods									
6	randomized trials	not serious	serious[c]	not serious	serious[d]	none	Compared to placebo, topiramate increased the percent-age of abstinence periods in two double-blind RCTs out of six studies	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

a. heterogeneous outcomes
b. the beneficial effects of the intervention appeared only in post hoc analysis of 2 RCTs, which was later contradicted by a Cochrane meta-analysis
c. same as a
d. same as

Table 3b. Topiramate
Author(s): Chan 2020
Question: Topiramate compared to placebo for Cocaine Use Disorders in patients with co-occurring opioid use disorders
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence for 3 or more weeks									
1	randomized trials	not serious	very serious[a]	not serious	not serious	none	the only RCT on topiramate vs placebo showed low-strength evidence for no effect on cocaine use or abstinence in cocaine users with comorbid OUD	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

a. not possible to show consistency since there is only one RCT studying this intervention

Table 3c. Topiramate

Author(s): Buchholz 2019

Question: Topiramate compared to Placebo for Cocaine Use Disorders

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
6	randomized trials	very serious[a]	serious[b]	serious[c]	not serious	none	Meta-analysis of 5 studies showed no significant differences in treatment retention but indicated that topiramate may increase abstinence. A more recent RCT subsequent to the meta-analysis showed reduction in quantity of cocaine used, frequency of use and money spent in the first 4 weeks but was equal to placebo at the end of the 12-week study.	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

a. narrative review, not systematic

b. heterogenous outcomes

c. no quantitative data available

Table 3d. Topiramate

Author(s): Chan 2019

Question: Topiramate compared to Placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
5	randomized trials	not serious	serious	not serious	not serious	none	27/100 (27.0%)	11/106 (10.4%)	**RR 2.56** (1.39 to 4.73)	**162 more per 1000** (from 40 more to 387 more)	⨁⨁⨁◯ Moderate	CRITICAL
Retention												
5	randomized trials	not serious	serious	not serious	not serious	none	206/305 (67.5%)	203/312 (65.1%)	**RR 1.01** (0.93 to 1.10)	**7 more per 1000** (from 46 fewer to 65 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Table 4. Naltrexone

Author(s): Buchholz 2019

Question: Naltrexone compared to Placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
2	randomized trials	very serious[a]	not serious	very serious[b]	serious[c]	none	Naltrexone did not improve cocaine use or drinks per day in one study and no differences in reduction in cocaine use were observed when comparing with placebo in the other one.	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

a. narrative review, not systematic

b. All studies included patients with co-occuring alcohol use disorders.

c. no quantitative data available

Table 5. Mirtazapine

Author(s): Buchholz 2019

Question: Mirtazapine compared to placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in substance use									
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	Small trial with patients with comorbid depression: there was no reduction in cocaine consumption compared to placebo	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

a. narrative review, not systematic

b. no quantitative data available

Table 6a. Methylphenidate
Author(s): Fluyau 2021
Question: Methylphenidate compared to Placebo for Cocaine Use Disorder
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in substance use									
3	randomized trials	not serious	not serious	not serious	serious[a]	none	methylphenidate pointed at a small reduction in cocaine use (SMD = 0.346, 95% CI: −0.080 to 0.771, P = 0.111), with no statistical significance. The results of this review specifically for this intervention show no difference in cocaine use.	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval
a. the main purpose of this review is to analyse pharmacological interventions as a whole and little data is gathered specifically for Methylphenidate in cocaine use disorder

Table 6b. Methylphenidate

Author(s): Chan 2020

Question: Methylphenidate compared to placebo for Cocaine Use Disorder in patients with co-occuring opioid use disorders

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate	placebo	Relative (95% CI)	Absolute (95% CI)		
Retention												
1	randomized trials	very serious[a]	very serious[b]	very serious[c]	not serious	none	18/30 (60.0%)	26/32 (81.3%)	**RR 0.74** (0.53 to 1.03)	**211 fewer per 1000** (from 382 fewer to 24 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

a. as described by the authors of this review

b. not possible to have consistency since there is only one RCT studying this intervention

c. this review aims to study psychostimulants as a whole, so there is not enough data specifically on methylphenidate

Table 6c. Methylphenidate

Author(s): Tardelli 2020

Question: Methylphenidate compared to placebo for adults with Cocaine Use Disorders

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate	placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
4	randomized trials	serious[a]	serious[b]	serious[c]	not serious	none	22/116 (19.0%)	23/110 (20.9%)	**RR 0.90** (0.60 to 1.37)	**21 fewer per 1000** (from 84 fewer to 77 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. High attrition rates in most of the studies and potential detection bias due to the behavioural effects of the medication that could hinder blinding.

b. the meta-analysis for this (methylphenidate) specific intervention shows heterogeneity when compared to overall prescription psychoestimulants

c. set combined trials on CUD and MUD populations

Table 7a. Modafinil

Author(s): Tardelli 2020

Question: Modafinil compared to placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
8	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	94/568 (16.5%)	52/357 (14.6%)	**RR 1.22** (0.83 to 1.77)	**32 more per 1000** (from 25 fewer to 112 more)	⨁(fr Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. high attrition and possible lost of blinding due to the effects of the medication
b. set combined trials on CUD and MUD populations
c. b. wide CI

Table 7b. Modafinil

Author(s): Buchholz 2019

Question: Modafinil compared to placebo for Cocaine Use Disorders

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
11	randomized trials	very serious[a]	serious[b]	not serious	very serious[c]	none	A meta-analysis reviewed 11studies (N = 896) comparing modafinil to placebo. Modafinil did not show benefits in abstinence rates. These data were influenced by one negative French study (N = 27) in which placebo outperformed modafinil (combined rate ratio 0.103, 95% CI: 0.015 – 0.706, P = 0.021). Authors specifically noted that high abstinence rates in the placebo group could have been influenced by the motivation for abstinence amongst patients willing to agree to extended inpatient treatment. Another subsequent subgroup analysis of studies conducted in the United States showed improved abstinence rates with modafinil over placebo (N =669, combined rate ratio 1.440, 95% CI: 1.027 – 2.020, P = 0.035).	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

a. characteristics of the population were not explained in this review, except for one RCT that involved a 17-day initial inpatient hospital stay and was conducted only in men without other SUDs

b. heterogeneity in outcomes across studies

c. wide confidence intervals

Table 8a. Prescription Amphetamines

Author(s): Chan 2020

Question: Prescription amphetamines compared to placebo for Cocaine Use Disorder with co-occurring opioid use disorders

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescription amphetamines	placebo	Relative (95% CI)	Absolute (95% CI)		
Cocaine-free urinalyses												
3	randomized trials	serious[a]	very serious[b]	very serious[c]	very serious[d]	none	73/115 (63.5%)	42/115 (36.5%)	**SMD 0.35** (-0.05 to 0.74)	**-- per 1000** (from -- to --)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

a. as described in the review
b. findings were mixed across studies and statistical heterogeneity was on the margin of significance (P = 0.05, I^2 =62%)
c. RCTs pooled with another intervention (mazindol), the weight of amphetamines being 52%
d. difference was not statistically significant (P = 0.08)

Table 8b. Prescription Amphetamines
Author(s): Chan 2019
Question: Prescription amphetamines compared to placebo for Cocaine Use Disorders
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
14	randomized trials	serious[a]	not serious	very serious[b]	not serious	none	Large body of evidence and consistent result but many trials were methodologically flawed. Findings from individual drugs favour dexamphetamine (small body of evidence) and mixed amphetamine salts (single study)	⊕◯◯◯ Very low	CRITICAL
Reduction in substance use									
8	randomized trials	serious[c]	serious[d]	very serious[e]	serious[f]	none	No difference. Use of cocaine, combined SMD 0.16 (95% CI: −0.02 to 0.33)	⊕◯◯◯ Very low	IMPORTANT
Retention									
24	randomized trials	serious[g]	not serious	very serious[h]	serious[i]	none	No difference. RR 1.00 (95%CI: 0.93 -- 1.06)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval

a. no data available
b. SR includes studies from psychostimulants as a whole group, with little information on specific medications
c. same as a
d. inconsistent results between trials
e. same as b
f. results trend towards positive but with no quantitative data
g. heterogeneous population
h. same as b

i. methodological limitations in the studies included, high number of participants who did not complete the trials.

Table 8c. Prescription Amphetamines

Author(s): Tardelli 2020

Question: Prescription amphetamines compared to placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prescription amphetamines	placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
7	randomized trials	serious[a]	not serious	not serious	not serious	none	91/316 (28.8%)	28/245 (11.4%)	**RR 2.44** (1.66 to 3.58)	**165 more per 1000** (from 75 more to 295 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. medication studied has behavioural effects that could be noticed by both patients and clinicians

Table 8d. Prescription Amphetamines

Author(s): Buchholz 2019

Question: Prescription amphetamines compared to placebo for Cocaine Use Disorder

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
4	randomized trials	not serious[a]	not serious	serious[b]	very serious[c]	publication bias strongly suspected[d]	Three randomized controlled trials (N = 154) = combined rate ratio 1.98, 95% CI: 1.12 – 3.52). Another RCT using oral dexamphetamine in treatment-refractory heroin and cocaine dependent individuals showed fewer days of cocaine use compared with placebo, mean 44.9 versus 60.6 days, respectively (P = 0.031; Cohen's standardized effect sized d = 0.58).	⨁.58 Very low	CRITICAL

CI: confidence interval

a. unclear

b. no characteristics of population available for most studies, the only one available being for treatment-refractory patients

c. small sample

d. narrative review

Table 9a. Bupropion
Author(s): Chan 2020
Question: Bupropion compared to placebo for Concurrent Use Disorder with co-occuring opioid use disorders
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Retention									
2	randomized trials	not serious[a]	not serious	very serious[b]	very serious[c]	none	There was evidence that antidepressants worsen treatment retention due to adverse effects.	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval
a. unclear - no data available
b. data available for antidepressants as a whole, with little information on the 2 bupropion trials
c. small sample for bupropion

Table 9b. Bupropion

Author(s): Chan 2019

Question: Bupropion compared to placebo for Cocaine Use Disorders

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
2	randomized trials	not serious[a]	not serious	not serious	extremely serious[b]	none	Favours bupropion. 1 SR of 2 RCTs reported a combined 3+ week abstinence RR of 1.63 (95% CI: 1.02 - 2.59)	⊕◯◯◯ Very low	CRITICAL
Retention									
3	randomized trials	not serious[c]	serious[d]	not serious	extremely serious[e]	none	No difference. The SR's combined RR for participants not completing the trial was 0.99 (95% CI: 0.79 - 1.25).	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval

a. unclear

b. very small sample

c. unclear

d. inconsistent results across studies

e. very small sample

Table 9c. Bupropion
Author(s): Buchholz 2019
Question: Bupropion compared to placebo for Cocaine Use Disorder
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
3	randomized trials	serious[a]	very serious[b]	serious[c]	serious[d]	none	One review including three RCTs found superiority of bupropion over placebo for cocainea bstinence (N = 176; combined rate ratio 1.63, 95%CI: 1.03 – 2.59). No differences were found for overall cocaine use, study retention or harms.	⊕.59 Very low	CRITICAL

CI: confidence interval
a. narrative review
b. mixed results across studies
c. no information on population studied
d. small sample

3.4.2. Methamphetamine reviews

Table 10a. Topiramate
Author(s): Nourredine 2021
Question: Topiramate compared to Placebo for MUD
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction in Drug use												
1	randomized trials	serious[a,b]	not serious	not serious	serious[c]	none	Topiramate did not signifcantly reduce the number of urine tests that were positive for drugs in weeks 6−12. How ever, in a subgroup analysis of 26 participants who were abstinent prior to the study, topiramate signifcantly prevented relapses in weeks 6−12.				⨁◯◯◯ Very low	IMPORTANT
Abstinence												
1	randomized trials	serious[a]	not serious	not serious	serious[c]	none	Rezaei et al. found that topiramate was associated with increased abstinence rates at week 6 but no longer at week 10. The authors did not provide an analysis of the entire study period.				⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

a. High attrition rates.
b. Unclear attrition rates; analysis of outcome during the entire study period not provided.
c. Data extracted from a single trial

Table 10b. Topiramate
Author(s): Siefried 2020
Question: Topiramate compared to placebo for MUD
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological	[comparação]	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
1	randomized trials	Serious[a]	not serious	not serious	serious[a]	none	No difference in abstinence.				⊕⊕◯◯ Low	CRITICAL

CI: confidence interval
a. high attrition rates
b. small sample

Table 11a. Mirtazapine
Author(s): Naji 2022
Question: Mirtazapine compared to Placebo for MUD
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mirtazapine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction in drug use (follow-up: 12 weeks)												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	37/65 (56.9%)	49/68 (72.1%)	**RR 0.81** (0.63 to 1.03)	**137 fewer per 1000** (from 267 fewer to 22 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Retention												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	77/90 (85.6%)	76/90 (84.4%)	**RR 1.01** (0.91 to 1.12)	**8 more per 1000** (from 76 fewer to 101 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio
a. Small number of events

Table 11b. Mirtazapine
Author(s): Siefried 2020
Question: Mirtazapine compared to Placebo for MUD
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
1	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	A study showed mirtazapine reduced MA use among MA-dependent sexually active men who have sex with men. The proportion of MA-positive UDS was significantly reduced in both study arms over time but was more pronounced and quicker in the mirtazapine (30 mg po OD) arm compared with the control arm.	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval

a. Data extracted from a single trial
b. Small sample size and number of events

Table 12a. Naltrexone

Author(s): Chan 2019a

Question: Natrexone compared to Placebo for MUD

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
1	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	1 RCT in MSM participants; limited applicability to general population	⊕ RC Very low	CRITICAL
Reduction in substance use									
4	randomized trials	serious[c]	very serious[d]	not serious	not serious	none	Inconsistent results and methodological limitations. Higher rate of negative UA in 1 low-ROB study, but no difference in 3 unclear-ROB studies.	⊕nco Very low	CRITICAL
Retention									
4	randomized trials	serious[e]	very serious[f]	not serious	not serious	none	No difference. Treatment retention naltrexone versus placebo: RR = 1.11, 95% CI = 0.88 – 1.41	⊕.41 Very low	IMPORTANT

CI: confidence interval

a. selection bias

b. small sample

c. unclear ROB

d. mixed results

e. same as c

f. mixed results. $I^2 = 61\%$

Table 12b. Naltrexone

Author(s): Chan 2020

Question: Naltrexone compared to Placebo for MUD - chan 2020

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
1	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	Treatment group had a greater percentage of negative UDS than placebo, but this difference was not statistically significant (40 % versus 24 %, P = 0.09).	⊕as Very low	CRITICAL
Retention									
1	randomized trials	very serious[c]	not serious	not serious	extremely serious[d]	none	(52 % treatment versus 28 % placebo, P = 0.01)	⊕ebo Very low	IMPORTANT

CI: confidence interval

a. changes to the protocol after study initiation

b. small sample and P = 0.09

c. same as a

d. small sample

Table 12c. Naltrexone
Author(s): Siefried 2020
Question: Naltrexone compared to placebo for MUD
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
5	randomized trials	serious[a]	serious[b]	not serious	not serious	none	Five studies examined the opioid antagonist naltrexone. Results of the studies are conflicting. There was no difference in MA use by UDS in the treatment arm compared with placebo in the extended-release studies. One study of naltrexone (a single 4-week injection) reported on 37 of 52 randomized participants and found a reduction in past 30-day MA use, but relied entirely on self-report, and there was a crossover in primary outcome measures given the past 30-day questionnaires were administered within 3 weeks of each other. One outpatient study of AMPH-dependent participants in Sweden reported fewer AMPH-positive UDS in the naltrexone (50 mg po OD) arm compared with placebo, a result shared by the study examining naltrexone implants (1000 mg subcutaneously) administered to Russian participants with AMPH dependence.	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval
Explanations
a. Most studies presented moderate to high attrition rates.
b. Conflicting results

Table 12d. Naltrexone

Author(s): Lam 2019

Question: Naltrexone compared to placebo for MUD

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
1	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	At trial completion, 7 of 50 participants in the naltrexone group and 10 of 50 participants in the placebo group had achieved abstinence. This difference was not significant.	⨁⨁◯◯ Low	CRITICAL
Reduction in drug use									
3	randomized trials	serious[c]	serious[d]	not serious	serious[a]	none	One study showed that the intention-to-treat analysis for the naltrexone group reported a significantly higher mean number of amfetamine-negative urine samples than the placebo group. The remaining studies reported no significant reduction in amfetamine use	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

a. Small sample and number of events

b. Data from a single trial.

c. High attrition rates in most of the included trials.

d. Inconsistent findings across trials.

Table 13a. Methylphenidate

Author(s): Chan 2019

Question: Methylphenidate compared to Placebo for MUD - chan 2019 meth

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in substance use									
4	randomized trials	very serious[a]	very serious[b]	not serious	very serious[c]	none	2 RCTs reported a positive effect on use, while 2 other RCTs found no difference.	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. high ROB as described by the author

b. mixed results

c. small sample

Table 13b. Methylphenidate

Author(s): Fluyau 2021

Question: Methylphenidate compared to Placebo for MUD and comorbid ADHD?

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
2	randomized trials	very serious[a,b]	not serious	not serious	very serious[c,d]	none	Two studies reported the outcome reduction on substance use, one with significant results (SMD = 0.66, [0.11, 1.21]) and another with no significant effect (SMD = 0.19, [0.11, -0.61, 0.99]). Both studies had relatively small sample sizes.	⨁◯◯◯ Very low	IMPORTANT
Abstinence									
1	randomized trials	very serious[a]	not serious	not serious	serious[d]	none	One study reported the outcome abstinence, with significant results (SMD = 0.22 [0.58, 1.03]). This study had very high attrition rates.	⨁◯◯◯ Very low	CRITICAL

SMD: standardized mean deviation

CI: confidence interval

a. Very high attrition rates in one of the studies

b. Reporting bias in one of the studies

c. Wide and inconclusive CIs.

d. Small sample size and number of events.

Table 13c. Methylphenidate

Author(s): Siefried 2020

Question: Methylphenidate compared to placebo for MUD

Setting:

Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
2	randomized trials	serious[a]	not serious	not serious	serious[b]	none	Two studies assessed reduction in methamphetamine use, both with non-significant results.	⨁⨁o Low	IMPORTANT

CI: confidence interval

a. One of the studies had concerning attrition rates.

b. Results reported only narratively.

Table 13c. Methylphenidate

Author(s): Tardelli 2020

Question: Methylphenidate compared to placebo for MUD

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate	placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	8/12 (66.7%)	9/12 (75.0%)	**RR 0.89** (0.53 to 1.49)	**82 fewer per 1000** (from 353 fewer to 368 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. This study had very high attrition rates.

b. Results came from a single trial with few individuals/events.

Table 14a. Modafinil
Author(s): Tardelli 2020
Question: Modafinil compared to placebo for MUD
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
8	randomized trials	serious[a]	serious[b]	not serious	not serious	none	94/568 (16.5%)	52/357 (14.6%)	RR 1.22 (0.83 to 1.77)	**32 more per 1000** (from 25 fewer to 112 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. High attrition rates
b. Inconsistent results across trials

Table 14b. Modafinil
Author(s): Siefried 2020
Question: Modafinil compared to placebo for MUD
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
3	randomized trials	serious[a]	not serious	not serious	serious[b]	none	None of the three studies demonstrated a difference in MA use, adherence or retention between study arms.	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval
Explanations
a. High attrition rates.
b. Small sample sizes/events.

Table 15. Prescription Amphetamines
Author(s): Siefried 2020
Question: Prescription Amphetamines compared to placebo for MUD
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in drug use									
1	randomized trials	serious[a]	not serious	not serious	Very serious[b,c]	none	One study reviewed 49 participants with MA dependence and prescribed 110 mg daily sustained-release oral dexamphetamine over 16 weeks. It measured MA use by self-report and analysis of hair, severity of dependence over time and treatment retention—finding no statistically significant difference between the study groups on planned analysis.	⨁◯◯◯ Very low	IMPORTANT
Abstinence									
1	randomized trials	not serious	not serious	not serious	very serious[b,c]	none	One study examined sustained-release oral dexamphetamine(30 mg po BD) for 60 MA-dependent participants. The primary outcomes included safety and efficacy defined as abstinence from MA—measured by a new MApositive UDS (measured twice weekly) and self-reported MA consumption. There was no significant difference between study groups on measures of MA consumption.	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval
a. High attrition rates.
b. Small sample/number of events.
c. Results came from a single trial.

Table 16. Bupropion
Author(s): Siefried 2020
Question: Bupropion compared to Placebo for MUD
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Abstinence									
4	randomized trials	serious[a]	not serious	not serious	serious[b]	none	None of the studies achieved a statistically significant difference in abstinence or reduction in use between the bupropion and placebo arm in planned primary outcome analyses.	⨁⨁nd Low	CRITICAL
Reduction in drug use									
2	randomized trials	serious[a]	not serious	not serious	serious[b]	none	None of the studies achieved a statistically significant difference in reduction in use between the bupropion and placebo arm in planned primary outcome analyses.	⨁⨁nd Low	IMPORTANT

CI: confidence interval
a. High attrition rates
b. No quantitative synthesis provided

3.5. Additional evidence not mentioned in GRADE tables

The six systematic reviews included for cocaine dependence assessed a wide range of outcomes that go beyond the ones reported at the GRADE tables above. As with abstinence and retention, the most reported outcomes, other outcomes also yielded heterogeneous results.

Reduction in cocaine use is reported by some of the reviews. Two reviews reported prescription amphetamines did not significantly reduce cocaine use[27,29]. The same was reported for topiramate[28], naltrexone, and bupropion[29]. Craving was assessed by two reviews: Fluyau and colleagues (2021) found that methylphenidate did not significantly reduce cocaine craving compared to placebo[30]; similarly, Buchholz and colleagues (2019) found Modafinil also did not reduce cocaine craving compared to placebo[28].
Finally, the review by Tardelli and colleagues found prescription psychostimulants (comprising prescription amphetamines, modafinil, and methylphenidate) promoted a slight but statistically significant increase in maximum continuous abstinence (MD = 3.34 days) as compared to placebo[16].

As for methamphetamine, eight reviews were included. Siefried and colleagues (2020) topiramate was not able to reduce craving or depressive symptoms in individuals with MUD[19]. Mirtazapine was also associated to reduction in depressive symptoms among individuals with MUD, but had no effect on number of sexual partners[21]. Prescription amphetamines could apparently reduce methamphetamine dependence symptoms and withdrawal/cravings, despite no statistically significant effects on outcomes such as abstinence and reduction in drug use[19].

Lam and colleagues (2019) found mixed results for the effect of naltrexone on methamphetamine craving, with two studies finding no statistically significant differences compared to placebo as opposite to one trial which found a significant effect of naltrexone for craving[32]. Similarly, Fluyau and colleagues (2021) found no effect of methylphenidate on methamphetamine craving[30], whereas Siefried and colleagues (2020) found one study with significant reduction in methamphetamine craving[19,33].

Trivedi and colleagues (2021) published a trial combining depot naltrexone and bupropion for the treatment of methamphetamine use disorder. This trial is more recent than the included reviews for naltrexone/bupropion for MUD. They found a statistically significant difference of 11.1% favouring the medication group for treatment response (3 negative methamphetamine urine samples out of the last four collected).

4. From Evidence to Recommendations

4.1. Summary of findings

Table 17. Summary of findings table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.gdiseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognized priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	Drug use and drug use disorders constitute a public health, developmental and security problem both in developed and developing countries worldwide. According to the latest global estimates, about 5.5 per cent of the population aged between 15 and 64 years have used drugs at least once in the past year, while 36.3 million people, or 13 per cent of the total number of persons who use drugs, suffer from drug use disorders (UNODC, 2021). Approximately 0.5 million deaths annually attributable to drug use (UNODC, 2021).	• Cocaine use is a relevant problem in many parts of the world, namely the Americas and Europe; • Methamphetamine use, in turn, is an increasing public health issue in North America and East and Southeast Asia.
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☒ **Small** ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	• Topiramate, prescription amphetamines, and bupropion have shown small desirable effects for cocaine dependence; • In turn, Mirtazapine, Naltrexone, and Methylphenidate have shown small desirable effects for methamphetamine dependence.	• Most of the trials were impacted by small samples and high dropout rates; • Most studies were conducted in first-world countries; • Prescription Amphetamines were not sufficiently assessed for the treatment of methamphetamine dependence; • Mirtazapine has shown promise for the

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				treatment of methamphetamine dependence among subgroups (trans women and men who have sex with men); further studies are warranted for different populations.
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☒ **Varies** ☐ Don't know	• Nearly all of the studies included found no significant differences between the assessed medicines and placebo in populations of patients with cocaine or methamphetamine dependence. The side effects found by this trial were mild for patients with MUD receiving naltrexone and bupropion. 3.6% reported serious side effects.	However, some medicines might have severe side effects and have potential for abuse (such as dexamphetamines, methylphenidate, modafinil) and require careful monitoring, which might be difficult to achieve in non-specialized settings
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates of effects	☐ Very low ☒ **Low** ☐ Moderate ☐ High ☐ No included studies	• Most of the outcomes studied had very low or low quality of evidence. • Topiramate and Prescription Amphetamines had moderate-quality evidence for promotion of abstinence among patients with cocaine dependence; • Mirtazapine had moderate-quality evidence for reduction in drug use and retention for methamphetamine dependence.	• Much of the evidence was hindered by high attrition rates; • Studies with prescription psychostimulants may have downgraded the evidence in one level due to the behavioural effect of the medicine (which would add detection bias)

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called "utility values".			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	*The qualitative review very briefly outlined the perceived benefits and attitudes of patients towards health outcomes. Some patients reported such incentives/benefits as improvement in health and positive perception of health along with positive changes in family.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgements regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☒ **Varies** ☐ Don't know	• In general, medicines had between trivial and small beneficial and adverse effects; • Topiramate, prescription amphetamines, and methylphenidate had a positive balance for cocaine dependence; Mirtazapine and had a positive balance for methamphetamine dependence.	•

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	they are)?			
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Don't know**		We did not find studies assessing costs of medicines and/or their implementation.
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**		We did not find studies assessing costs of medicines and/or their implementation and therefore cannot assess certainty of evidence.

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgements regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☒ **No included studies**	No reviews examining cost effectiveness identified	We did not find studies assessing costs of medicines and/or their implementation and therefore cannot assess cost-effectiveness.
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritize and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☒ **Don't know**		• We did not find studies assessing the impact of medicines on equity, equality, and non-discrimination. • Mirtazapine was tested in sexual minorities with compelling results. This could have an impact reducing inequalities.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?			
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know		Even though no studies on feasibility were available, we assume medicine implementation should probably be feasible depending on resource availability.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socioculturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know		Even though no studies on accordance with human rights were available, we assume a voluntary medicine-centred model should be aligned with human rights and culturally acceptable in most societies.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?			

4.2. Summary of judgements

Table 18. Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	✓ **Small**	- Moderate	- Large
Undesirable effects	- Don't know	✓ **Varies**		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence	- No included studies			- Very low	✓ **Low**	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	- No important uncertainty or variability
Balance of effects	- Don't know	✓ **Varies**	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Resources required	✓ **Don't know**	- Varies	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Equity, equality and non-discrimination	✓ **Don't know**	- Varies	- Reduced	Probably reduced	- Probably no impact	- Probably increased	- Increased
Feasibility	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes
Human rights and sociocultural acceptability	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes

✓Indicates category selected, -Indicates category not selected

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Appendix I: mhGAP process note

mhGAP Guideline Update: Notes on process for identifying level of evidence review required v2_0 (13/12/2021)

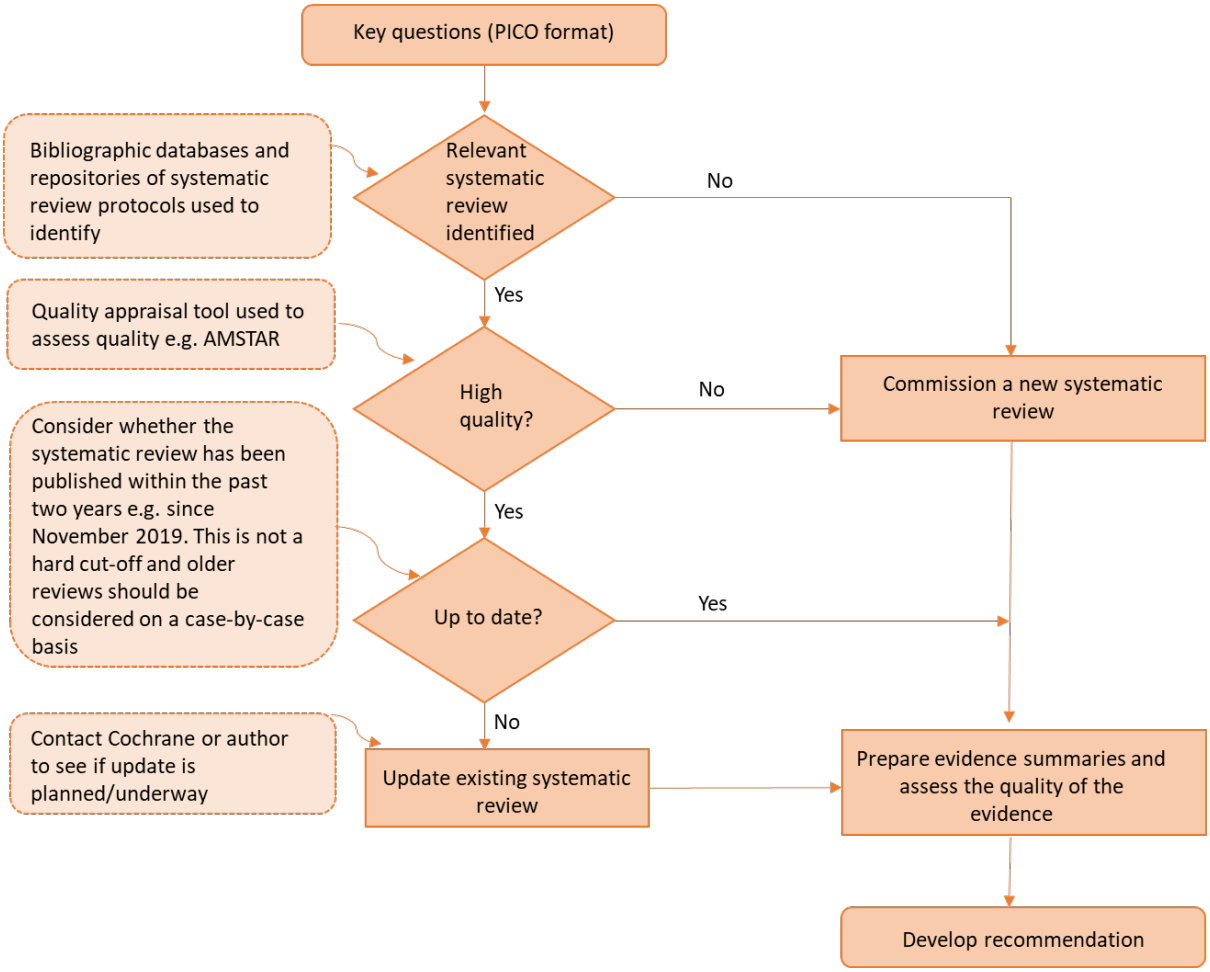
This document is intended to provide guidance to focal points on the level of evidence review required as part of the evidence retrieval process for the mhGAP guideline update process. As a general rule, the update process should be informed by existing high quality systematic reviews.
The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714.

Three main categories of evidence review are proposed in this document:

1) Existing relevant, up to date, high quality systematic review(s) provide the evidence required. **An existing systematic review is sufficient to prepare the evidence summaries**. It may be possible to include more than one systematic review for the same PICO, as different reviews may match different outcomes of a PICO. However, if more than one systematic review is available for the same PICO outcome, one review should be selected, based on quality, relevance, search comprehensiveness and date of last update. The selection process should be transparently reported, with justification of choices.
2) Existing high quality systematic reviews are either out of date or do not fully address the PICO, though it is considered that the review can be updated to meet these requirements. **An update of an existing systematic review is required before the evidence summaries can be prepared**. The update process may require addition of new studies published after the review, or inclusion of outcomes not covered by the existing reviews.
3) Existing systematic reviews are either not of sufficiently high quality or cannot be updated to fully address the PICO. **A new systematic review is required before the evidence summaries can be prepared**

Figure 1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

Fig. 1. Is a new systematic review needed



All key questions are currently in PICO format as presented in the Appendix of the planning proposal PICOs. Subsequent steps include the following:

1. **Identify and evaluate existing systematic reviews**: Identify one or more systematic review(s) to address each PICO question. Existing systematic reviews will inform the guideline development process, whether or not a new systematic review or an update of an existing review is required, and the evidence review team will detail existing systematic reviews in each case. The method for identifying existing systematic reviews should be fully detailed in the evidence summary and include the following sources:
    a. Search of bibliographic databases, such as PubMed/MEDLINE, Embase, PsychInfo, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHIL, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus.
    b. Search of repositories of systematic reviews protocols, including PROSPERO, Open Science Framework (OSF), and Cochrane.
2. **Assess if systematic review is up to date:** It is preferred that identified systematic reviews have been published within the past two years e.g. since November 2019. This is not a hard cut-off and older reviews should be considered on a case-by-case basis, particularly those covering the time period since the last update of the mhGAP guideline in 2015. It is acknowledged that COVID has led to a pausing of many mental health research activities over the past two years, and this may also impact the availability of systematic reviews within the preferred two year period. For any reviews that fall outside the two year period, the guideline methodologist will advise on suitability.

3. **Appraise quality of systematic review:** Use the AMSTAR-2 quality appraisal tool to assess the quality of the identified systematic review(s) https://amstar.ca/docs/AMSTAR-2.pdf . This includes consideration of the extent to which the PICO is fully addressed by the systematic review(s) identified.

By following the process outlined in figure 1, and steps 1-3 above, the FP and evidence review team will have sufficient evidence to assess which of the three main categories of evidence review apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

Appendix II: AMSTAR evaluation of the included systematic reviews

Buchholz 2019

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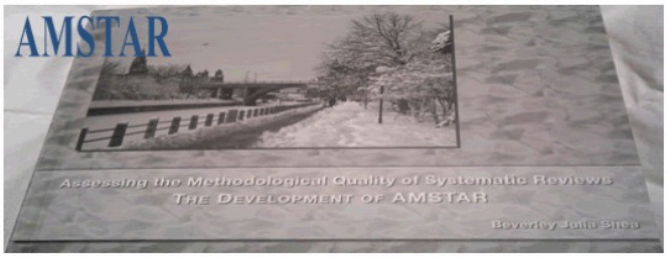

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AMSTAR 2 Results

Printer Friendly Version

Article Name: Buchholz 2019

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Buchholz 2019 is a Critially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No

7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	No
NRSI	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	0
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Chan 2019

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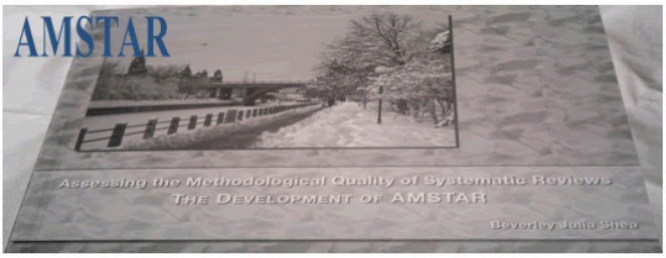

AMSTAR 2 Results

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Article Name: Chan 2019

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Chan 2019 is a Critially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	No
NRSI	0 Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Chan 2019a (methamphetamine)

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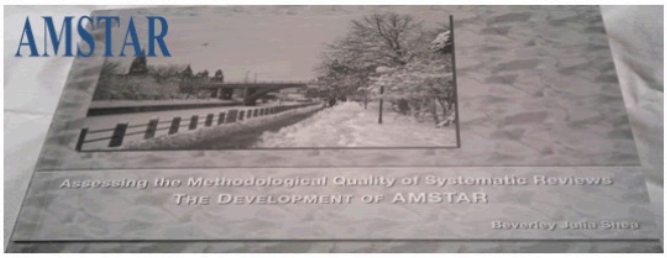

AMSTAR 2 Results

Printer Friendly Version

Article Name: Chan 2019a

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Chan 2019a is a Critially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the	Yes

exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	No
NRSI	0 Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Chan 2020

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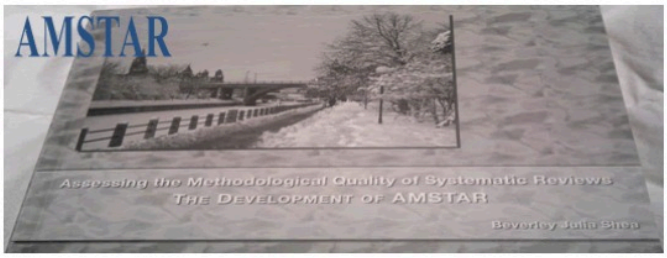

AMSTAR 2 Results

Printer Friendly Version

Article Name: Chan 2020

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Log On

Chan 2020 is a Critially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	No
NRSI	0 Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Fluyau 2021

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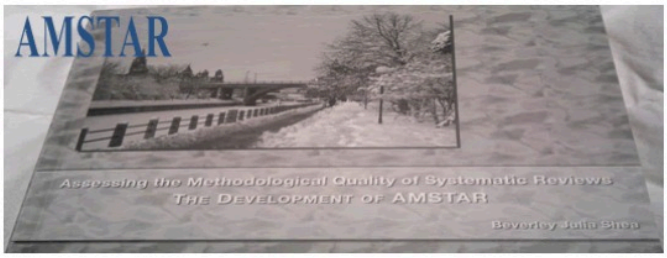

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Printer Friendly Version

Article Name: Fluyau 2021

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Fluyau 2021 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	0 Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes Yes Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Lam 2019

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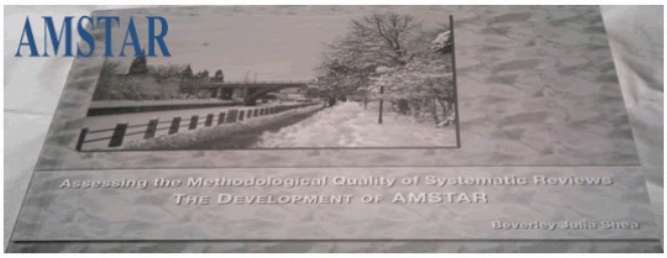


AMSTAR Checklist

Printer Friendly Version

Article Name: Lam 2019

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- [x] Population
- [x] Intervention
- [x] Comparator group
- [x] Outcome

Optional (recommended)
- [ ] Timeframe for follow up

- [x] Yes
- [ ] No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- [ ] review question(s)
- [ ] a search strategy
- [ ] inclusion/exclusion criteria
- [ ] a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- [ ] a meta-analysis/synthesis plan, if appropriate, and
- [ ] a plan for investigating causes of heterogeneity
- [ ] a plan for investigating causes of heterogeneity

- [ ] Yes
- [ ] Partial Yes
- [x] No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- [ ] Explanation for including only RCTs
- [ ] OR Explanation for including only NRSI
- [ ] OR Explanation for including both RCTs and NRSI

- [ ] Yes
- [x] No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

For Yes, should also have (all the following):

- [x] searched at least 2 databases (relevant to research question)
- [x] provided key word and/or search strategy
- [x] justified publication restrictions (e.g. language)
- [ ] searched the reference lists / bibliographies of included studies
- [ ] searched trial/study registries
- [ ] included/consulted content experts in the field
- [ ] where relevant, searched for grey literature
- [x] conducted search within 24 months of completion of the review

- [ ] Yes
- [x] Partial Yes
- [ ] No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- [ ] at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- [x] OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- [x] Yes
- [ ] No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- [ ] at least two reviewers achieved consensus on which data to extract from included studies
- [x] OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- [x] Yes
- [ ] No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- [ ] provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- [x] Justified the exclusion from the review of each potentially relevant study

- [x] Yes
- [ ] Partial Yes
- [ ] No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- [x] described populations
- [x] described interventions
- [x] described comparators
- [x] described outcomes
- [x] described research designs

For Yes, should also have ALL the following:

- [x] described population in detail
- [x] described intervention in detail (including doses where relevant)
- [x] described comparator in detail (including doses where relevant)
- [x] described study's setting
- [x] timeframe for follow-up

- [x] Yes
- [ ] Partial Yes
- [ ] No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- [x] unconcealed allocation, and

For Yes, must also have assessed RoB from:

- [x] allocation sequence that was not truly random, and

- [x] Yes
- [ ] Partial Yes
- [ ] No

☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☑ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, and	☐ methods used to ascertain exposures and outcomes, and	☐ Yes ☐ Partial Yes ☐ No ☑ Includes only RCTs
☐ from selection bias	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☑ No meta-analysis conducted

For NRSI

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☑ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☑ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

☐ included only low risk of bias RCTs	☑ Yes

☐ No

☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

☐ There was no significant heterogeneity in the results

☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☑ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☑ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

☑ The authors reported no competing interests OR

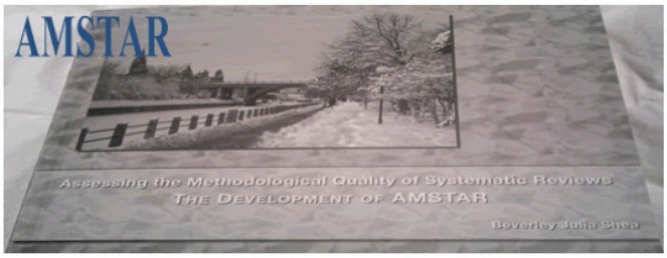
☐ The authors described their funding sources and how they managed potential conflicts of interest

☑ Yes
☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Assess Article

Naji 2022



AMSTAR 2 Results

Printer Friendly Version

Article Name: Naji 2022

Naji 2022 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the	No

exclusions?	
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	0 Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

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To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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Nourredine 2021

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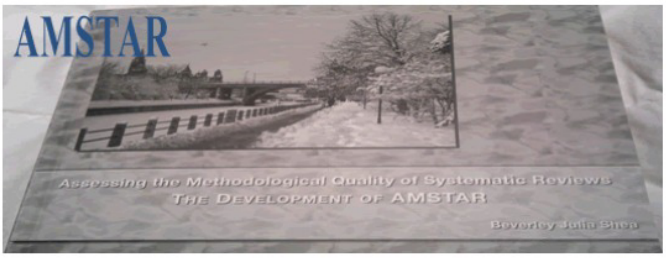

AMSTAR 2 Results

Printer Friendly Version

Article Name: Nourredine 2021

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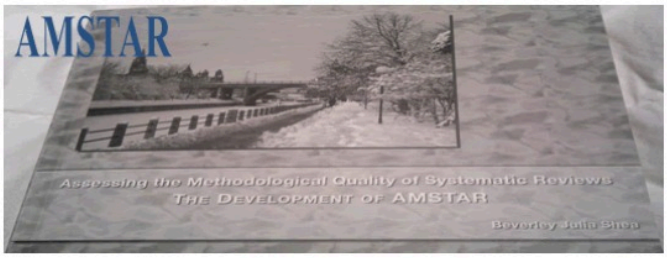
Nourredine 2021 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	0
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

Siefried 2020



AMSTAR 2 Results

Printer Friendly Version

Article Name: Siefried 2020

Siefried 2020 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the	No

exclusions?	
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	0
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Tardelli 2020

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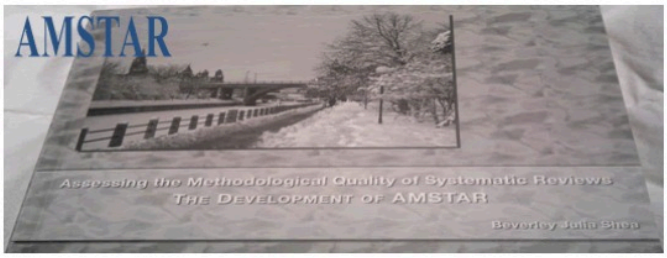

AMSTAR 2 Results

Printer Friendly Version

Article Name: Tardelli 2020

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Tardelli 2020 is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	0 Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

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