Q2: In patients with complaints of depressive symptoms (in absence of current/prior depressive episode/disorder) are anti-depressants or benzodiazepines better (more effective in symptom reduction in the short-term [immediate] or long-term [>6 months]) and as safe as usual care?

Background

Most patients with depressive episodes receive care in the general practice, where depression may be intended in terms of fluctuating mood disturbances occurring in response to life situations and difficulties, insecure relationships and deprivation. Many such patients in this setting just fail to reach the minimum diagnostic criteria for major depression, and are described as having minor or subsyndromal or subthreshold depression (SD).

The notion that SD represents a clinical and public health issue is based on the following grounds. First, SD is associated with psychological suffering and with significant impairment in daily living activities, with a considerable impact on the quality of life of patients. Second, SD is a strong risk-factor for major depression, which develops in 10-25% of patients with SD within 1 to 3 years; additionally, SD might increase the risk of death in older individuals. Third, despite treatment guidelines recommend to prescribe antidepressant medicines to individuals with moderate to severe major depression only, under ordinary circumstances patients with depressive symptoms that fail to reach the minimum diagnostic criteria for major depression are “at high risk” of receiving antidepressant treatment.

Epidemiological data have consistently shown that the focusing of antidepressant therapy, i.e. the proportion of patients that are prescribed antidepressants according to evidence-based criteria, is very low: in the province of Alberta, Canada, for example, more than 67% of a community sample of individuals receiving antidepressants did not have any MINI diagnosis, but reported, as the main reasons for taking these medicines, depressive symptoms, stress, sleep problems, anxiety, headache (Esposito et al, 2007). It is therefore possible that in recent years the threshold of antidepressant prescribing has progressively decreased and that individuals with subthreshold conditions have been more often exposed to treatment.

Currently there is uncertainty on whether antidepressants or other pharmacological treatments have a favourable risk-benefit profile in individuals with SD.

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

Population: patients with minor or subsyndromal depression (complaints of depressive symptoms in absence of depressive episode)

Interventions: antidepressants or benzodiazepines

Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)

Comparison: placebo*

Outcomes: symptom reduction

adverse events

**(only available - though imperfect - proxy for usual care)*

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Literatures searches were performed in the following databases and article indexes:

- MEDLINE
- CINAHL
- EMBASE
- PsycInfo
- Cochrane Controlled Trials Register

Controlled vocabulary was utilized where appropriate terms were available, supplemented with keyword searches to ensure accurate and exhaustive results. Search results were limited to Randomized Controlled Trials or Clinical Trials (Phase III). Language or Publication Year limits were not applied to any search.

To illustrate, the following MEDLINE search is indicative of searches performed in the other databases. It should be noted that although searches across the databases were similar, there are database-specific tools and terms that were utilized to ensure effective retrieval.

#1 Depression/Drug therapy [MeSH] OR Depressive Disorder [MeSH]/exp

#2 subthreshold depression OR minor depression OR mild depression OR subsyndromal depression OR non-major depression

Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)

#3 Benzodiazepines [MeSH]/exp

#4 Antidepressants [MeSH]/exp OR Antidepressant Agents [MeSH]/exp

#5 #1 OR #2

#6 #5 AND #3

#7 #5 AND #4

#8 #5 AND #3 AND #4

#9 #6 OR #7 OR #8 AND Limits: Randomized Controlled Trial, Clinical Trial, Phase III.

To supplement the searches of published research, the Internet was also utilized to locate additional clinical trials, unpublished research and/or grey literature. Websites of pharmaceutical companies, clinical trials, and medical control agencies were searched with a specific focus on clinical trial registries.

Searched Websites include:

- Clinical Trials.gov http://clinicaltrials.gov/ct/gui

- Eli Lilly: www.lilly.com

- Lundbeck: www.lundbeck.com

- Organon: www.organon.com

- Solvay: www.solvay.com

- Pfizer: www.pfizer.com

Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)

- GlaxoSmithKline: www.gsk.com

- Bristol Myers Squibb: www.bms.com

- Pierre Fabre : www.pierre-fabre.com

- Wyeth: www.wyeth.com

- Food and Drug Administration (USA): www.fda.gov

- European Medicines Agency (EU): www.emea.europa.eu

- Pharmaceuticals and Medical Devices Agency (Japan): www.pmda.go.jp

- Therapeutic Goods Administration (Australia): www.tga.gov.au

Narrative description of the studies that went into the analysis

A total of more than 716 articles were identified by the search process. Two reviewers identified 6 articles of studies involving anti-depressants meeting the review criteria. No trials were identified involving benzodiazepines in minor/sub-threshold depression.

Barrett et al (2001)

Methods	Eleven weeks, double-blind, randomized study.
Participants	Primary care patients meeting DSM-III-R research criteria for minor depression (3 of the 9 DSM-III-R symptoms for major depression, 1 of these had to be depressed mood or anhedonia). The PRIME-MD, a diagnostic instrument designed for use in primary care, was used to make diagnoses. Age range:18-59.

	Subjects were excluded if they were found to have major depression.
Interventions	Paroxetine: 38 participants. Placebo: 39 participants. Paroxetine dose: 10-40 mg/day.
Outcomes	Remission rates defined as a Hamilton Depression Rating Scale score of less than 7.
Notes	Funding: John A. Hartford Foundation of New York and the MacArthur Foundation.
Reference	Barrett JE et al (2001). Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years. *Journal of Family Practice,* 50:405-12.

Burrows et al (2002)

Methods	Eight weeks, double-blind, randomized study.
Participants	Inpatients of a long-term care facility with non-major depression. Age range: 80-97. Subjects were excluded if they were found to be actively suicidal, psychotic, or to have major depression.
Interventions	Paroxetine: 12 participants. Placebo: 12 participants. Paroxetine dose: 10-30 mg/day.
Outcomes	17-item Hamilton Depression Rating Scale. Responders: Clinical Global Impression of 1 or 2.
Notes	Funding: SmithKline Beecham Pharmaceuticals.
Reference	Burrows AB et al (2002). A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. *Depression and Anxiety,* 15:102-10.

Davidson et al (1988)

Methods	Six weeks, double-blind study.

Participants	Outpatients meeting RDC criteria of minor depression. Age range: 18-65.
Interventions	Isocarboxazid: 19 participants. Placebo: 16 participants. Isocarboxazid dose: 49.3 mg/day at week 6.
Outcomes	Responders: Clinical Global Impression of 1 or 2.
Notes	Funding: Hoffmann La Roche.
Reference	Davidson JR et al (1988). An efficacy study of isocarboxazid and placebo in depression, and its relationship to depressive nosology. *Archives of General Psychiatry,* 45:120-7.

Judd et al (2004)

Methods	Twelve weeks, double-blind, randomized study.
Participants	Outpatients with minor depression according to the National Institute of Mental Health Diagnostic Interview Schedule (DIS). Age range: 18 years or older Subjects were excluded if they were found to have major depression.
Interventions	Fluoxetine: 81 participants. Placebo: 81 participants. Fluoxetine dose: 10-20 mg/day (more than 90% received 20 mg/day).
Outcomes	17-item Hamilton Depression Rating Scale.
Notes	Three authors were employed by Eli Lilly & Co., Indianapolis. Funding: NIMH, Roher Fund of the University of California, Eli Lilly.

Reference	Judd LL et al (2004). Randomized, placebo-controlled trial of fluoxetine for acute treatment of minor depressive disorder. *American Journal of Psychiatry,* 161:1864-71.

Paykel et al (1988)

Methods	Six weeks, double-blind, randomized study.
Participants	General practitioners' patients meeting RDC criteria for minor depression. Age range: 18-64.
Interventions	Amitriptyline: 19 participants. Placebo: 18 participants. Amitriptyline dose: mean 119 mg/day (week 6).
Outcomes	17-item Hamilton Depression Rating Scale.
Notes	Funding: Medical Research Council.
Reference	Paykel ES et al (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders,* 14:83-95.

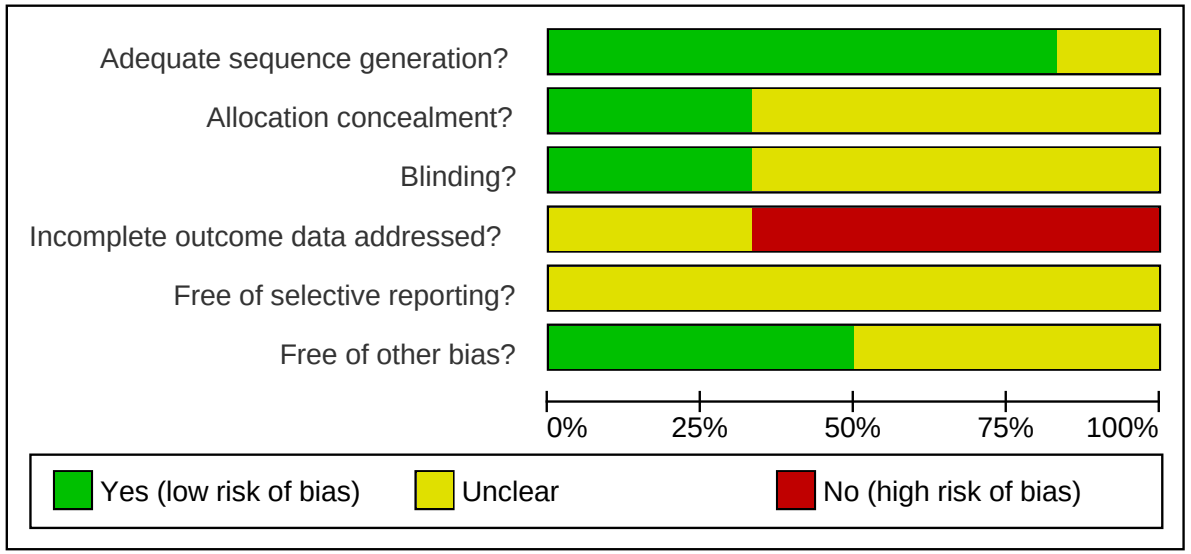
Williams et al (2000)

Methods	Eleven weeks, double-blind, randomized study.
Participants	Primary care patients meeting DSM-IV research criteria for minor depression. The PRIME-MD, a diagnostic instrument designed for use in primary care, was used to make diagnoses. Age range:60 years or older. Subjects were excluded if they were found to have major depression.
Interventions	Paroxetine: 68 participants. Placebo: 70 participants. Paroxetine dose: 10-40 mg/day.

Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)

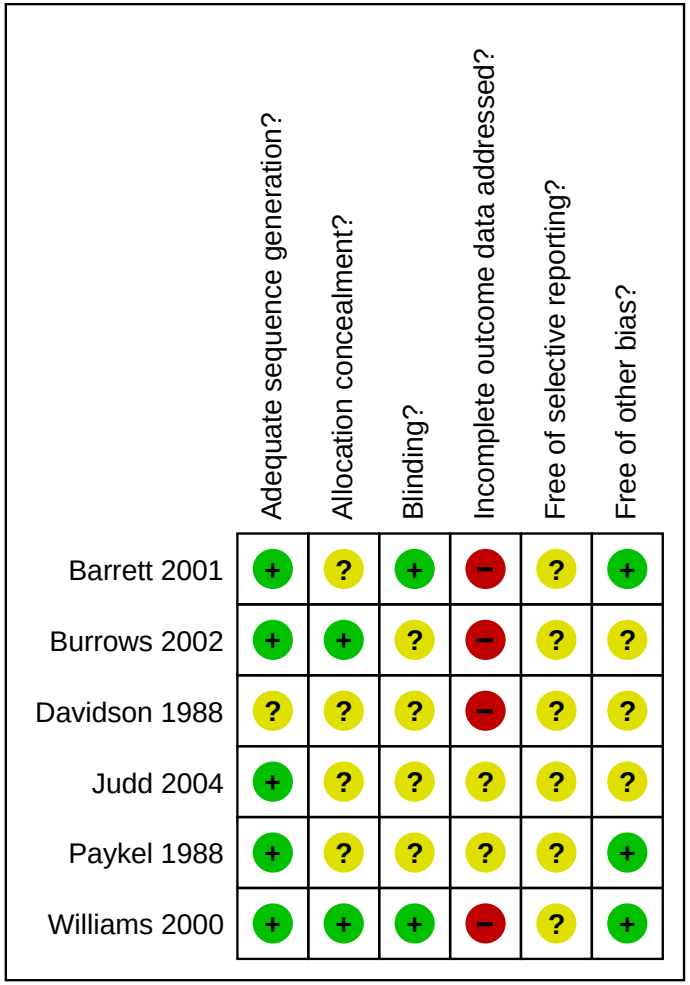
Outcomes	Remission rates defined as a Hamilton Depression Rating Scale score of less than 7.
Notes	Funding: John A. Hartford Foundation of New York and the MacArthur Foundation.
Reference	Williams JW Jr et al (2000). Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. *Journal of the American Medical Association*, 284:1519-26.

Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies



Methodological quality summary: review authors' judgments about each methodological quality item for each included study

[Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)]

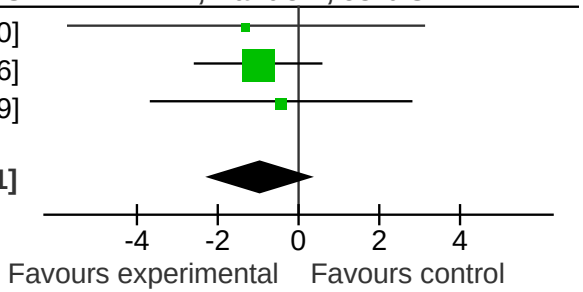


Analysis 1.1. Depressive symptoms

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Burrows 2002	8.9	5	9	10.2	5	11	9.3%	-1.30 [-5.70, 3.10]
Judd 2004	7.1	5	78	8.1	5	79	73.4%	-1.00 [-2.56, 0.56]
Paykel 1988	6.86	5	19	7.29	5	18	17.3%	-0.43 [-3.65, 2.79]
Total (95% CI)			**106**			**108**	**100.0%**	**-0.93 [-2.27, 0.41]**

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.36 (P = 0.17)

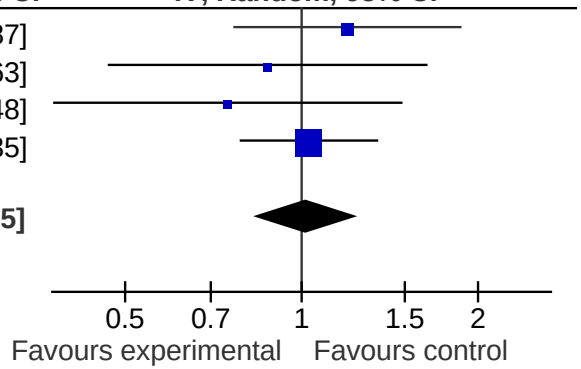


Analysis 1.2. Proportion of patients failing to improve

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Barrett 2001	21	38	18	39	21.4%	1.20 [0.77, 1.87]
Burrows 2002	7	12	8	12	10.8%	0.88 [0.47, 1.63]
Davidson 1988	8	19	9	16	9.0%	0.75 [0.38, 1.48]
Williams 2000	42	68	42	70	58.8%	1.03 [0.79, 1.35]
Total (95% CI)		**137**		**137**	**100.0%**	**1.01 [0.83, 1.25]**
Total events	78		77			

Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 3 (P = 0.68); I² = 0%

Test for overall effect: Z = 0.14 (P = 0.89)

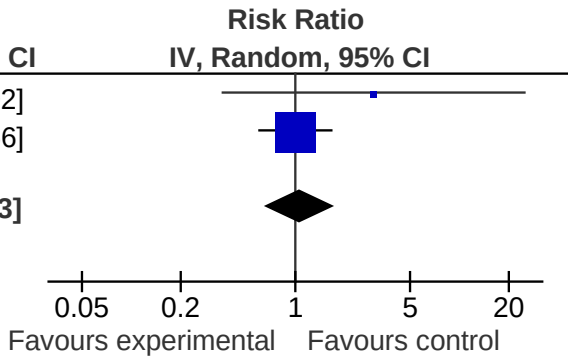


Analysis 1.3. Proportion of patients failing to complete the study

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Burrows 2002	3	12	1	12	5.4%	3.00 [0.36, 24.92]
Judd 2004	22	81	22	81	94.6%	1.00 [0.60, 1.66]
Total (95% CI)		**93**		**93**	**100.0%**	**1.06 [0.65, 1.73]**
Total events	25		23			

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); I² = 0%

Test for overall effect: Z = 0.24 (P = 0.81)



GRADE Tables

Table 1

Author(s): C Barbui, M van Ommeren
Date: 2009-08-06
Question: Should antidepressants vs placebo be used for subthreshold depression/minor depression?
Settings:
Bibliography: Burrows AB et al (2002). A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. *Depression and Anxiety,* 15:102-10.

Judd LL et al (2004). Randomized, placebo-controlled trial of fluoxetine for acute treatment of minor depressive disorder. *American Journal of Psychiatry,* 161:1864-71.

Paykel ES et al (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders,* 14:83-95.

Quality assessment	Summary of findings			Importance
	No of patients	Effect	Quality	

Anti-depressants or benzodiazepines in patients with complaints of depressive symptoms (in absence of depressive episode/disorder)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressants	placebo	Relative (95% CI)	Absolute		
symptom reduction (follow-up mean 8.6 weeks; measured with: Hamilton Depression Rating Scale (17 items); Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106	108	-	MD 0.93 lower (2.27 lower to 0.41 higher)[2]	⊕⊕OO LOW	CRITICAL
failure to respond (follow-up mean 8.3 weeks)												
4	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/137 (56.9%)	77/137 (56.2%)	RR 1.01 (0.83 to 1.25)	6 more per 1000 (from 96 fewer to 141 more)	⊕⊕OO LOW	CRITICAL
functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
development of depressive episode												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
treatment acceptability (follow-up mean 10 weeks)												
2	randomised trials	no serious limitations	serious[4]	no serious indirectness	serious	none	25/93 (26.9%)	23/93 (24.7%)	RR 1.06 (0.65 to 1.73)	15 more per 1000 (from 87 fewer to 181 more)	⊕⊕OO LOW	IMPORTANT

[1] All three included studies were described as randomized, double blind and placebo controlled. However, in one study dropout rates were not reported, and in two studies standard deviations were lacking. One study recruited individuals with both major and minor depression, and reported results separately.

[2] One additional randomized trial compared sertraline with treatment as usual in older individuals with subthreshold depression (Brenes et al (2007).This study did not employ a placebo arm for comparison, and did not employ a double-blind technique (although outcome assessment was masked). It randomized 11 patients to sertraline and 12 to usual care. In terms of depressive symptoms, after 4 months of follow-up, sertraline produced a non-significant advantage over treatment as usual (MD -0.66, 95% confidence interval -1.50 to 0.18).

[3] All four included studies were described as randomized, double blind and placebo controlled. However, in three studies dropout rates were not reported, and in all four studies it is not clear how incomplete outcome data were managed. One study recruited individuals with both major and minor depression, and reported results separately. Two studies recruited individuals with both minor depression and dysthymia, and reported results separately.

[4] Although the I-squared revealed no heterogeneity, visual inspection of the forest plot suggested some inconsistency.

Reference List

Barrett JE et al (2001)Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years. *Journal of Family Practice,* 50:405-12.

Brenes GA et al (2007). Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. *Aging and Mental Health,* 11:61-8.

Burrows AB et al (2002). A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. *Depression and Anxiety,* 15:102-10.

Davidson JR et al (1988). An efficacy study of isocarboxazid and placebo in depression, and its relationship to depressive nosology. *Archives of General Psychiatry,* 45:120-7.

Esposito E et al (2007). Frequency and adequacy of depression treatment in a Canadian population sample. *Canadian Journal of Psychiatry,* 52:780-9.

Judd LL et al (2004). Randomized, placebo-controlled trial of fluoxetine for acute treatment of minor depressive disorder. *American Journal of Psychiatry,* 161:1864-71.

Paykel ES et al (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders,* 14:83-95.

Williams JW Jr et al (2000). Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. *Journal of the American Medical Association*, 284:1519-26.

From evidence to recommendations

Factor	Explanation
Narrative summary of	In terms of symptom reduction after acute treatment (8.6 weeks) there is evidence suggesting there is unlikely to be a

the evidence base	clinically important difference between antidepressants and placebo (the mean difference between antidepressants and placebo is less than 1 point at the 17-item HDRS). In terms of proportion of individuals showing an improvement in depressive symptoms, there is evidence suggesting there is unlikely to be a clinically important difference between antidepressants and placebo (absolute risk difference of less than 1%). In terms of functioning no evidence was available. In terms of proportion of individuals developing a depressive episode no evidence was available. In terms of treatment dropouts the evidence is inconclusive and so it is not possible to determine if there is a clinically important difference between antidepressants and placebo. No trials were identified involving benzodiazepines in minor/sub-threshold depression.
Summary of the quality of evidence	The quality of evidence was MODERATE for symptom reduction and LOW for responders and dropouts.
Additional evidence that was not included in GRADE tables or context evidence not directly related to the scoping question	Benzodiazepines is associated with risk of dependence. The safety of psychotropics in pregnancy and breastfeeding is not clearly established. In particular, exposure to benzodiazepines during the first trimester is associated with an increased risk of oral clefts, and exposure during the third trimester is associated with neonatal difficulties. For antidepressants, the risks of taking tricyclic antidepressants during pregnancy and when breastfeeding are better established than those of SSRIs and newer drugs. Antidepressants appeared not to be teratogenic, although SSRI exposure in late pregnancy may increase the risk of persistent pulmonary hypertension.
Balance of benefits versus harms	See above.
Values and preferences including any variability	In situations where people are exposed to severe ongoing social stressors (e.g. domestic abuse), disorder may be difficult to differentiate from a transient reaction. Clinicians should assess psychosocial stressors (e.g. domestic abuse,

and human rights issues	unemployment) associated with depressive symptoms and include appropriate psychosocial interventions in their treatment plan.
Costs and resource use and any other relevant feasibility issues	Training is required to properly recognise complaints of depressive symptoms in absence of depressive episode/disorder with due attention to any cultural variations in depression that may exist. In many low and middle income countries, continuous availability of psychotropics in non-specialized health care is a challenge. Both tricyclic antidepressants and many selective serotonin reuptake inhibitors are associated with low acquisition costs. Amitriptyline (as a representative of the tricyclic antidepressants), fluoxetine and diazepam are included in the WHO list of essential medicines for the treatment of depressive disorders.

Final recommendation(s)

Neither antidepressants nor benzodiazepines should be used for the initial treatment of individuals with complaints of depressive symptoms in absence of current/prior depressive episode/disorder.

Strength of recommendation: STRONG

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

NICE National Clinical Guideline Number 123. Common Mental Health Disorders. National Institute for Health and Clinical Excellence, 2011