South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Mirtazapine for the treatment of Major Depressive Disorder (MDD) for the specific population groups

Date: updated July 2023 (previous NEMLC recommendation November 2022)

Key findings

- There are medicine treatment options for Major Depressive Disorder at Adult Hospital Level (SSRIs and TCAs) and Tertiary and Quaternary Hospital Level (SNRIs or atypical antidepressants). However, there may be specific populations that may benefit from mirtazapine as an alternative option.
- We conducted a rapid review of systematic reviews, meta-analyses and clinical trials reporting on the efficacy and safety of mirtazapine in four specific populations groups (four PICOs). We identified 5 studies for inclusion and data was presented narratively.
- ***PICO 1 – cardiac patients with depression because of its favourable cardiac side effect profile – (1 systematic review of 29 RCTs, n = 4974)***

Number of participants with hypertension or tachycardia

- There were fewer participants with hypertension or tachycardia in mirtazapine compared to TCAs (OR 0.44, 95% CI 0.24 to 0.81, P=0.01; i2=0%; 4 studies, n=552), review found no studies reporting on hypertension or tachycardia for mirtazapine compared to SSRIs or SNRIs

Number of participants with hypotension or bradycardia

- There were fewer participants with hypotension or bradycardia for mirtazapine compared to TCAs (OR 0.46, 95% CI 0.12 to 1.81, P=0.86; i2=0%; 2 studies, n=215) and compared to SSRIs (OR 1.04 95% CI 0.77 to 1.41, P = 0.79; i2=30.85%; 10 studies, n=2658), review found no studies reporting on hypotension and bradycardia for mirtazapine compared to SNRIs.

Number of participants with dizziness or vertigo or faintness

- There were more participants with dizziness, vertigo or faintness for mirtazapine compared to TCAs (OR 3.04 95% CI 0.59 to 15.53, P = 0.18; i2=30.85%; 7 studies, n=1166), no difference compared to SNRIs (OR 0.19 95% CI 0.02 to 1.68, P=0.14; 1 study, n=157) but more participants reported for mirtazapine compared to SSRIs (OR 5.41, 95% CI 0.61 to 47.62, P=0.13; 1 studies, n=137)

- ***PICO 2 – Oncology patients who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects - (1 systematic review of 29 RCTs, n = 4974, 1 systematic review of 12 RCTs and observational studies)***

Number of participants with weight gain or increase in appetite

- No difference found between mirtazapine and TCAs for weight gain and increased appetite (OR 1.04, 95% CI 0.58 to 1.86, P = 0.89; i2=29.05%; 3 studies, n=463).

Number of participants with sleep disturbance

- There were more participants with sleep disturbance in mirtazapine compared to TCAs (OR 1.43, 95% CI 0.69 to 2.98, P=0.34; 1 study, n=207).

Number of participants with sleepiness/drowsiness/somnolence

- No difference found between mirtazapine and TCAs for sleepiness/drowsiness/somnolence (OR 0.92, 95% CI 0.66 to 1.27, P = 0.07; i2=70.57%; 6 studies, n=941).

- ***PICO 3 – As a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs – 1 RCT, n=150***

Number of participants achieving score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17)

- There was a higher percentage of participants with a score of 7 or less for venlafaxine-XR compared to mirtazapine (mirtazapine n=20 (36.4%) vs venlafaxine-XR n=21 (42%); P=0.578) and for paroxetine compared to mirtazapine (mirtazapine n=20 (36.4%) vs paroxetine n=21 (46.7%); P=0.578).

- ***PICO 4 – As an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression, 2 RCTs, n=684***

Mean difference in the Beck Depression Inventory (BDI-II) score after 12 weeks (higher score = more severe depression)

- There was a lower mean score for mirtazapine plus usual care (SNRI or SRRI) compared to usual care alone (MD -1.83, 95% CI -3.92 to 0.27, P=0.087, n=480).

Change in HAMD-17 score from baseline to 6 weeks (higher score = more severe depression)

- There was a larger change from baseline for mirtazapine plus paroxetine compared to paroxetine alone (mean difference in change from baseline 0.77, 95% CI -1.86 to 3.39, P=0.6175).
- Another RCT reported that combination therapy of SSRI and mirtazapine showed significant improvement in HAMD-17 score at week 6 (p =0.006) and week 8 (p = 0.013) compared to SSRI monotherapy, n=154)

Categorical response rate (CGI improvement score criteria and 50% reduction in HRSD-17)

- At end point categorical response rate was 64% for mirtazapine augmentation, and 20% response rate for placebo, p = 0.043.

Remission rates

- Remission rates were 45.4% for mirtazapine augmentation compared to 13.3% for placebo in on small study however results were not significant, p = 0.068.

Overall quality of evidence was evaluated to be low quality – systematic reviews of moderate quality, some concerns with risk of bias for RCTs, small sample sizes, indirectness of evidence.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Rationale: The Tertiary and Quaternary Hospital Level Expert Review Committee recommends against the inclusion of mirtazapine for the specified population groups due to limited direct evidence to demonstrate superiority over standard of care.

Level of Evidence: Low quality
Review indicator: Change in evidence

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

Mirtazapine is a noradrenergic specific serotonergic antidepressant utilised for Major Depressive Disorder. Some data has shown that it may be equivalent or superior to selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and Tricyclic antidepressants (TCAs) and that the adverse event profile may be unique[1,2].

The current standard of care for adults for major depressive disorder at regional hospital level are SSRIs e.g.: oral fluoxetine, or citalopram if fluoxetine is poorly tolerated. If a sedating antidepressant is required amitriptyline (TCA) is indicated. At Tertiary and Quaternary Level, bupropion (atypical antidepressant) or venlafaxine (SNRI) are recommended as third line agents (currently venlafaxine is awarded on contract due to price).

A motivation was received from the Western Cape Pharmaceutical and Therapeutics Committee proposing the inclusion of mirtazapine on the essential medicines list for the management of major depression in the following populations:

- Cardiac patients with depression because of the favourable cardiac side effect profile
- Oncology patients who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects.
- As a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs.
- As an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression.

RESEARCH QUESTION: Should Mirtazapine be included on the Essential Medicines List (EML) for use in Major Depressive Disorder (MDD) for the specific patient groups (see PICOs)?

Eligibility criteria for review

PICO 1: Cardiac patients with depression because of the favourable cardiac side effect profile	
Population	Cardiac patients with major depressive disorder
Intervention	Mirtazapine
Comparator/s	Selective Serotonin Reuptake Inhibitors (SSRIs); Tricyclic antidepressant (TCAs); Serotonin-norepinephrine reuptake inhibitor (SNRIs)
Outcome/s	**Safety** – Any adverse event; cardiovascular adverse events

PICO 2: Oncology patients who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects.	
Population	Oncology patients with Major Depressive Disorder who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects.
Intervention	Mirtazapine
Comparator/s	Tricyclic antidepressant (TCAs)
Outcome/s	**Efficacy** – Reduction in depressive symptoms with response to treatment or remission as measured by the HAM-D-17, and/or the MADRS, and/or Beck Self Rating Depression Scale, and/or the Brief Psychiatric Rating Scale. **Safety** – Adverse events

PICO 3: As a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs.	
Population	Patients with Major Depressive Disorder who have cannot tolerate or have failed on SSRIs/SNRIs/TCAs
Intervention	Mirtazapine
Comparator/s	Atypical antidepressants (buproprion only atypical approved)
Outcome/s	**Efficacy** – Reduction in depressive symptoms with response to treatment or remission as measured by the HAM-D-17, and/or the MADRS, and/or Beck Self Rating Depression Scale, and/or the Brief Psychiatric Rating Scale. **Safety** – Adverse events

PICO 4: As an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression.	
Population	Patients with treatment resistant Major Depressive Disorder
Intervention	Mirtazapine plus SSRI or SNRI
Comparator/s	SSRI or SNRI alone
Outcome/s	**Efficacy** – Reduction in depressive symptoms with response to treatment or remission as measured by the HAM-D-17, and/or the MADRS, and/or Beck Self Rating Depression Scale, and/or the Brief Psychiatric Rating Scale. **Safety** – Adverse events

Study designs: Randomized controlled trials and systematic reviews.

METHODS

A rapid search of evidence was conducted in PubMed and the Cochrane Library in September 2022. Limited studies were found that directly matched the study PICO (population sub-groups) thus the search was expanded to mirtazapine for major depression in adults and the best available evidence for each PICO will be presented. The search strategy is outlined in Appendix 2. Screening and selection of articles were conducted independently by two reviewers (JR and GG). Data extraction was conducted by two reviewers (JR and KM) and reviewed by the ERC. An AMSTAR 2 assessment was conducted independently and in duplicate on the selected systematic reviews (KM and JR). Selected RCTs were assessed for risk of bias by one reviewer (KM).

RESULTS

Results of the search

The search produced 722 results. After title and abstract screening 36 articles underwent full text review. Five studies were included for data extraction and summarised narratively below (See Appendix 3 – Characteristics of included studies). A summary of the excluded studies can be found in Appendix 4.
Following an appeal received post review finalisation, and additional 2 systematic reviews and meta-analyses were considered. These reviews did not meet the PICOs, however 2 studies included in the one review were added, as they aligned with PICO 4.

Description of studies included

PICO 1 – Cardiac patients with major depressive disorder

One systematic review of randomised controlled trials (RCTs) was included which reported on cardiac related safety outcomes/adverse events:

- Watanabe et al. (2011)[2] conducted a Cochrane systematic review of RCTs (29 RCTs, n = 4974) exploring the safety and efficacy of mirtazapine (any dose) versus other antidepressants (TCAs, SNRIs, SSRIs, heterocyclic antidepressants) for individuals aged 18 years or older, with depression. A number of tolerability and acceptability outcomes were evaluated.

PICO 2 – Oncology patients with major depressive disorder who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects.

The systematic review included under PICO 1 were also evaluated in terms of sedation and weight gain side-effects. In addition, one systematic review of RCTs and observational studies was included:

- Economos et al. (2020)[3] carried out a systematic review of clinical trials (12 trials, n=392), exploring mirtazapine in combination or alone compared to other treatments for cancer related symptoms such as weight gain in oncology patients with depression.

PICO 3 – Mirtazapine as a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs.

One RCT was included for this specific PICO:

- Fang et al. (2010)[4] reported on a double-blind RCT on individuals 18 years or older (n=150) with major depressive disorder classified as treatment resistant (failed or inadequately responded to two or more antidepressants from different classes). The study explored the efficacy and tolerability of 45mg/day mirtazapine (n=55), 225mg/day extended-release venlafaxine (n=50) and 20mg/day paroxetine (n=45). Primary outcome was remission rate at 8 weeks defined by the Hamilton Rating Scale for Depression 17-item (HRSD-17) total score of 7 or smaller.

PICO 4 – Mirtazapine as an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression.

Four studies were included for this specific PICO:

- Kessler et al. (2018)[5] conducted a double-blind RCT as a part of Health Technology Assessment on individuals with depression aged 18 years or older (n=480) with an inadequate response to an SSRI or SNRI after six weeks of treatment. The study compared mirtazapine in addition to usual care of an SSRI or SNRI (n= 241) to usual care and placebo (n=239). The primary outcome was change in the Beck Depression Inventory (BDI-II) score after 12 weeks.
- Xiao et al. (2021)[6] conducted a double-blind RCT on individuals aged 18-60 years (n=204) with major depressive disorder and early non-response to paroxetine (after two weeks in an open-label phase). Thereafter individuals were randomly assigned to into a mirtazapine and placebo group (n = 68), paroxetine and placebo group (n = 68) or mirtazapine and paroxetine group (n = 68). The primary outcome was improvement on the Hamilton Rating Scale for Depression 17-item (HRSD-17) scores after 6 weeks.
- Carpenter et al. (2002)[7] conducted a double-blind RCT on 26 patients with persistent major depression despite adequate antidepressant monotherapy. Patients were randomised to either mirtazapine 15mg augmentation (n = 11) of placebo (n = 15) for 4 weeks. The primary antidepressants were SSRIs, but 1 patient was on bupropion and 1 on venlafaxine. The outcomes of categorical response (CGI improvement score criteria and 50% reduction in HRSD-17) and remission were measured at week 4.
- Kato et.al. (2017)[8] conducted an open-label randomised on individuals aged 20-75 years with major depressive disorder (n = 154). Individuals were randomised to receive mirtazapine or SSRI in step 1 for 4 weeks. Non-responders in step 1 were randomly assigned to either mirtazapine, or SSRI monotherapy or combination for 4 weeks. The primary efficacy outcome was a change in HAM-D 17 from baseline to week 4 for step 1 and from week 4 to week 8 for step 2.

Effects of Interventions

PICO 1 - Cardiac patients with major depressive disorder (1 systematic review of 29 RCTs, n = 4974[2])

Comparison 1: Mirtazapine versus TCAs

Outcome 1.1 Number of participants with hypertension or tachycardia:
The review reported that less participants developed hypertension or tachycardia in the mirtazapine groups compared to TCA groups (OR 0.44, 95% CI 0.24 to 0.81, P=0.01; i^2=0%; 4 studies, n=552) – Appendix 6 Figure 1.

Outcome 1.2 Number of participants with hypotension or bradycardia:
The review found that there were less participants in the mirtazapine groups developed hypotension or bradycardia than in the TCA groups however results were not statistically significant (OR 0.46, 95% CI 0.12 to 1.81, P=0.86; i^2=0%;2 studies, n=215 - Appendix 6 Figure 2

Outcome 1.3 Number of participants with dizziness or vertigo or faintness:
The review reported that more participants in the mirtazapine groups developed dizziness, vertigo or faintness compared to the TCA groups however results were not statistically significant (OR 3.04 95% CI 0.59 to 15.53, P = 0.18; i^2=30.85%; 7 studies, n=1166) - Appendix 6 Figure 3

Comparison 2: Mirtazapine versus SSRIs

Outcome 2.1 Number of participants with hypertension or tachycardia:
The review reported that no data was available for hypertension or tachycardia for this comparison.

Outcome 2.2 Number of participants with hypotension or bradycardia:
Only one study was included in the review and reported that more participants developed hypotension or bradycardia in the mirtazapine groups however results were not statistically significant (OR 5.41, 95% CI 0.61 to 47.62, P=0.13; 1 studies, n=137) - Appendix 6 Figure 4

Outcome 2.3 Number of participants with dizziness or vertigo or faintness:
The review found no difference in participants developing dizziness, vertigo or faintness between mirtazapine and SSRI groups (OR 1.04 95% CI 0.77 to 1.41, P = 0.79; i^2=30.85%; 10 studies, n=2658) - Appendix 6 Figure 5

Comparison 3: Mirtazapine versus SNRIs

Outcome 3.1 Number of participants with hypertension or tachycardia:
The review reported that no data was available for hypertension or tachycardia for this comparison.

Outcome 3.2 Number of participants with hypotension or bradycardia:
Only one study was included in the review and reported that more participants developed hypotension or bradycardia in the SNRI group compared to the mirtazapine group however results were not statistically significant (OR 0.19 95% CI 0.02 to 1.68, P=0.14; 1 study, n=157) – Appendix 6 Figure 6

Outcome 3.3 Number of participants with dizziness or vertigo or faintness:
The review reported that no data was available for dizziness, vertigo or faintness for this comparison.

PICO 2 - Oncology patients with major depressive disorder who do not tolerate SSRIs/SNRIs and who would benefit from the sedation and weight gain side effects (1 systematic review of 29 RCTs, n = 4974[2], 1 systematic review of 12 RCTs and observational studies)

Comparison 1: Mirtazapine versus TCAs

Outcome 1.1 Number of participants with weight gain or increase appetite:
The review found no difference between mirtazapine and TCA groups in participants developing weight gain or increased appetite (OR 1.04, 95% CI 0.58 to 1.86, P = 0.89; i^2=29.05%; 3 studies, n=463) – Appendix 6 Figure 7

Outcome 1.2 Number of participants with sleep disturbance:
The review reported that more participants who developed sleep disturbance in the mirtazapine group compared to the TCA group however results were not statistically significant (OR 1.43, 95% CI 0.69 to 2.98, P=0.34; 1 study, n=207).

Outcome 1.3 Number of participants with sleepiness/drowsiness/somnolence:
The review found no difference between mirtazapine and TCA groups in participants who developed sleepiness, drowsiness or somnolence (OR 0.92, 95% CI 0.66 to 1.27, P = 0.07; i^2=70.57%; 6 studies, n=941).

Comparison 2: Mirtazapine versus other antidepressants

A systematic review of clinical trials evaluating evidence for mirtazapine in cancer-related symptomatology, including depression, weight gain and appetite. Quality of evidence was graded as very low for all three symptoms (Depression - 8 studies, n=249; Weight gain - 4 studies, n=148; Appetite – 3 studies, n=113 – very low certainty, large concern regarding risk of bias)[3].

PICO 3 - As a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs (1 RCT, n=150)

Comparison 1: Mirtazapine versus venlafaxine-XR (SNRI)

Outcome 1.1 Number of participants achieving score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17): The double blinded RCT found a higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the venlafaxine-XR group compared to the mirtazapine groups but results were not significant (mirtazapine n=20 (36.4%) vs venlafaxine-XR n=21 (42%); P=0.578).

Comparison 2: Mirtazapine versus paroxetine (SRRI)

Outcome 2.1 Number of participants achieving score of 7 or less on the HRSD-17: The double blinded RCT found a higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the paroxetine group compared to the mirtazapine groups but results were not significant (mirtazapine n=20 (36.4%) vs paroxetine n=21 (46.7%); P=0.578).

PICO 4 - As an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression (4 RCTs, n=815[5,6])

Comparison 1: Mirtazapine plus usual care (SRRI/SNRI) versus usual care and placebo

Outcome 1.1 Mean difference in the Beck Depression Inventory (BDI-II) score after 12 weeks (higher score = more severe depression)

The Kessler et al. study reported that the mean BDI-II score was lower in the mirtazapine plus usual care (SRRI or SNRI) group compared to the usual care alone group however results were not significantly different (MD -1.83, 95% CI -3.92 to 0.27, P=0.087, n=480)[5].

Outcome 1.2 Categorical positive response rate (CGI change score of "much improved" or "very much improved" and 50% or greater reduction in HRSD-17 total score after 4 weeks.

Carpenter et al. found that the categorical response rate at end point was 64% for mirtazapine augmentation, and 20% response rate for placebo, p = 0.043[7].

Outcome 1.3 Remission rates (defined as week 4 HRSD-17 score less than 8).

Remission rates were 45.4% for mirtazapine augmentation compared to 13.3% for placebo in the Carpenter et al. study however results were not significant, p = 0.068[7].

Outcome 1.4 Change in HAM-D 17 (Hamilton Depression Rating) after 4 weeks

Kato et al. 2017 reported that combination therapy of SSRI and mirtazapine showed significant improvement in HAM-D score at week 6 (p =0.006) and week 8 (p = 0.013) compared to SSRI monotherapy[8].

Comparison 2: Mirtazapine plus paroxetine (SRRI) versus paroxetine and placebo

Outcome 2.1 Change in HAMD-17 score from baseline to 6 weeks (higher score = more severe depression)

Xiao et al. reported that the mean change from baseline was larger in the mirtazapine plus paroxetine group (13.27) compared to the paroxetine and placebo group (12.50) but not significantly different (mean difference in change from baseline 0.77, 95% CI -1.86 to 3.39, P=0.6175). Significant differences were reported in HAMD-17 scores between groups at baseline however analyses conducted to explore impact did not alter the direction of the results)[6].

Quality of the Evidence

Both systematic reviews were evaluated to be of moderate quality utilising the AMSTAR 2 checklist (See Appendix 5). Limitations of the Watanabe *et al*.[2] Cochrane review included a lack of explanation for study design criteria and that a quantitative analysis of potential publication bias was not conducted however the study was carried out in 2011 where this type of analysis may not have been as common. Although full text review was conducted independently in duplicate, screening was only carried out by one reviewer. The Economos *et al*.[3] systematic review also did not provide reasoning for inclusion or exclusion of certain study designs. Furthermore, the review did not describe the source of funding for selected studies. Although data extraction was specified to be conducted in duplicate this was not specified for study selection.

There was some concern with risk of bias for all the included RCTs. There were no concerns regarding randomisation for Fang *et al.*[4] but both Kessler *et al*.[5] and Xiao *et al.*[6] reported significant differences at baseline for key characteristics such as depression severity. However, randomisation in both studies was conducted remotely with satisfactory methods for allocation concealment. Participants and individuals delivering the intervention were blinded in all studies. Although Fang *et al*. did not specify that outcome assessors were blinded, randomisation was conducted by an independent statistical unit and details on the dummy packaging of the intervention and controls fully described. All studies utilised intention-to-treat analyses. More than 10% of outcome data was missing in the Fang *et al*. and Xiao *et al*. RCTS, however adequate sensitively analyses were applied and indicated that this do not affect the overall results. All studies had protocols with prespecified analysis plans, and all results were reported.

Evidence for the PICOs was very limited and most of the data did not directly match the PICOs. In addition, samples sizes were generally small. Overall, the evidence was considered to be of low quality

COSTS

Cost of medicines/ month:

Medicine	**Cost (ZAR) per month**
Mirtazapine 15mg daily	R306.93* / R213.86**
Mirtazapine 30mg daily	R463.18* / R324.97**
Mirtazapine 45mg daily	R770.10* / R538.83**
Fluoxetine 20mg daily	R6.44 #
Citalopram 20mg daily	R8.66 #
Amitriptyline 25mg – 150mg daily	R6.60-R27.64 #
Venlafaxine 37.5 - 150mg daily	R31.63 – R121.69 #

**average SEP: August 2022, **Lowest SEP: August 2022, # National contract price: October 2022*

CONCLUSION

For PICO 1, there was no evidence to suggest a superiority of mirtazapine for bradycardia, hypotension, dizziness, vertigo or faintness. Despite some evidence to demonstrate superiority of mirtazapine over TCAs in terms of patients with tachycardia or hypertension as an adverse event, evidence showing superiority over SSRIs and SNRIs was not available. Quality of the evidence was considered as low and costs are expected to be more intensive. The ERC thus did not recommend mirtazapine for inclusion for cardiac patients with depression.

For PICO 2, there was no evidence to suggest a superiority of mirtazapine for weight gain or increased appetite over TCAs. Quality of the evidence was considered as low and costs are expected to be more intensive. The ERC thus did not recommend mirtazapine for inclusion for oncology patients intolerant to SRRIs or SNRIs.

For PICO 3, there was no evidence to suggest a superiority of mirtazapine over paroxetine (SSRI) or venlafaxine-XR (SNRI) for reduction in depression severity. Quality of the evidence was considered as low

and costs are expected to be more intensive. The ERC thus did not recommend mirtazapine for inclusion as a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs.

For PICO 4, there was conflicting evidence to suggest the superiority of mirtazapine in addition to usual care (SSRI/SNRI) for reduction in depression severity, some studies show significant improvements, while others showed non-significant improvements (assessment time frames for studies showing significant improvements were short time frames, 4 weeks). There was no evidence to suggest the superiority of mirtazapine in addition to paroxetine (SSRI) over paroxetine alone for reduction in depression severity. Quality of the evidence was as low and costs are expected to be more intensive. The ERC thus did not recommend mirtazapine for inclusion as an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression.

Reviewers: G Grobler, K MacQuilkan, J Riddin,

Declaration of interests:

- Dr G Grobler (Clinical Psychiatry Unit, Steve Biko Academic Hospital) Consultant on GEMS Medical Scheme Expert Psychiatry Panel.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare.
- Ms K MacQuilkan (Right to Care) has no interests to declare.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Quality of evidence was evaluated to be low due to some concerns with risk of bias, indirectness of evidence and small sample sizes.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	**PICO 1 - Cardiac patients** – 1 Systematic review *Comparison 1: Mirtazapine versus TCAs* No. with hypertension or tachycardia: Fewer participants in the mirtazapine groups (OR 0.44, 95% CI 0.24 to 0.81, P=0.01; i2=0%; 4 studies, n=552) No. with hypotension or bradycardia: Less participants in the mirtazapine groups (OR 0.46, 95% CI 0.12 to 1.81, P=0.86; i2=0%;2 studies, n=215 No. with dizziness or vertigo or faintness: More participants in the mirtazapine groups (OR 3.04 95% CI 0.59 to 15.53, P = 0.18; i2=30.85%; 7 studies, n=1166). *Comparison 2: Mirtazapine versus SSRIs* No. with hypotension or bradycardia: More participants in the mirtazapine groups (OR 5.41, 95% CI 0.61 to 47.62, P=0.13; 1 studies, n=137) No. with dizziness or vertigo or faintness: No difference between mirtazapine and SSRI groups (OR 1.04 95% CI 0.77 to 1.41, P = 0.79; i2=30.85%; 10 studies, n=2658) *Comparison 3: Mirtazapine versus SNRIs* No. with hypotension or bradycardia: More participants in the SNRI group compared to the mirtazapine group (OR 0.19 95% CI 0.02 to 1.68, P=0.14; 1 study, n=157) **PICO 2 - Oncology patients** – 2 Systematic reviews *Comparison 1: Mirtazapine versus TCAs* No. with weight gain or increase appetite: No difference between mirtazapine and TCA groups (OR 1.04, 95% CI 0.58 to 1.86, P = 0.89; i2=29.05%; 3 studies, n=463) No. with sleep disturbance: More participants in the mirtazapine group compared to the TCA group (OR 1.43, 95% CI 0.69 to 2.98, P=0.34; 1 study, n=207). No. with sleepiness / drowsiness / somnolence: No difference between mirtazapine and TCA groups (OR 0.92, 95% CI 0.66 to 1.27, P = 0.07; i2=70.57%; 6 studies, n=941).

		PICO 3 - As a third line agent for depression in patients who have not responded/tolerated SSRIs/SNRIs/TCAs (1 RCT, n=150) *Comparison 1: Mirtazapine versus venlafaxine-XR (SNRI)* No. achieving score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17): Higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the venlafaxine-XR group compared to the mirtazapine groups (mirtazapine n=20 (36.4%) vs venlafaxine-XR n=21 (42%); P=0.578). *Comparison 2: Mirtazapine versus paroxetine (SRRI)* No. achieving score of 7 or less on the HRSD-17: Higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the paroxetine group compared to the mirtazapine groups (mirtazapine n=20 (36.4%) vs paroxetine n=21 (46.7%); P=0.578). **PICO 4 - As an augmentation agent in combination with SSRI or venlafaxine for treatment resistant depression (4 RCTs, n=815)** *Comparison 1: Mirtazapine plus usual care (SRRI/SNRI) versus usual care and placebo* Mean difference in the Beck Depression Inventory (BDI-II) score after 12 weeks (higher score = more severe depression) • The mean BDI-II score was lower in the mirtazapine plus usual care (SRRI or SNRI) group compared to the usual care alone group (MD -1.83, 95% CI -3.92 to 0.27, P=0.087, n=480). • Another study found that the categorical response rate at end point was 64% for mirtazapine augmentation, and 20% response rate for placebo, p = 0.043. Remission rates were 45.4% for mirtazapine augmentation compared to 13.3% for placebo in the Carpenter et al. study however results were not significant, p = 0.068[7]. • The third RCT reported that combination therapy of SSRI and mirtazapine showed significant improvement in HAM-D score at week 6 (p =0.006) and week 8 (p = 0.013) compared to SSRI monotherapy. *Comparison 2: Mirtazapine plus paroxetine (SRRI) versus paroxetine and placebo* Change in HAMD-17 score from baseline to 6 weeks (higher score = more severe depression) The mean change from baseline was larger in the mirtazapine plus paroxetine group (13.27) compared to the paroxetine and placebo group (12.50) (mean difference in change from baseline 0.77, 95% CI -1.86 to 3.39, P=0.6175).

<table>
<tr><td>QUALITY OF EVIDENCE OF HARM</td><td>What is the certainty/quality of evidence?
High [ ] Moderate [ ] Low [X] Very low [ ]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>Low quality evidence.</td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
Large [ ] Moderate [ ] Small [X] None [ ]</td><td>Overall, small effect size</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control or Uncertain [X]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR) per month</th></tr><tr><td>Mirtazapine 15mg daily</td><td>R306.93* / R213.86**</td></tr><tr><td>Mirtazapine 30mg daily</td><td>R463.18* / R324.97**</td></tr><tr><td>Mirtazapine 45mg daily</td><td>R770.10* / R538.83**</td></tr><tr><td>Fluoxetine 20mg daily</td><td>R6.44 #</td></tr><tr><td>Citalopram 20mg daily</td><td>R8.66 #</td></tr><tr><td>Amitriptyline 25mg – 150mg daily</td><td>R6.60-R27.64 #</td></tr><tr><td>Venlafaxine 37.5 - 150mg daily</td><td>R31.63 – R121.69 #</td></tr></table>*average SEP: August 2022, **Lowest SEP: August 2022, # National contract price: October 2022</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [ ] Uncertain [X]</td><td></td></tr>
</table>

Appendix 2: Search Strategy

PubMed

Search	Query	Search Details	Results
#6	#5 [filters human, +19 years, systematic reviews and meta-analyses]	("mirtazapine"[MeSH Terms]) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (humans[Filter]) AND (alladult[Filter]))	14
#5	#5 [filters human, +19 years, systematic reviews , RCTS and meta-analyses]	("mirtazapine"[MeSH Terms] AND ("depressive disorder"[MeSH Terms] OR ("depressive disorder, major"[MeSH Terms] OR "depressive disorder"[MeSH Terms]) OR "depression"[Title/Abstract])) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (humans[Filter]) AND (alladult[Filter]))	138
#4	#4 AND #5 [Filters human, +19 years, systematic reviews and meta-analyses]	("mirtazapine"[MeSH Terms] AND ("depressive disorder"[MeSH Terms] OR ("depressive disorder, major"[MeSH Terms] OR "depressive disorder"[MeSH Terms]) OR "depression"[Title/Abstract])) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (humans[Filter]) AND (alladult[Filter]))	12
#3	#4 AND #5	"mirtazapine"[MeSH Terms] AND ("depressive disorder"[MeSH Terms] OR ("depressive disorder, major"[MeSH Terms] OR "depressive disorder"[MeSH Terms]) OR "depression"[Title/Abstract])	721
#5	mirtazapine	"mirtazapine"[MeSH Terms]	1 462
#4	Major Depressive Disorder	"depressive disorder"[MeSH Terms] OR "depressive disorder, major"[MeSH Terms] OR "depressive disorder"[MeSH Terms] OR "depression"[Title/Abstract]	440 260
#3	Treatment resistant	(Mirtazapine[MeSH Terms]) AND (depression, treatment resistant[MeSH Terms])	9
#2	Cardiovascular patients	(Mirtazapine) AND (Cardiovascular)	88
#1	Oncology patients	(Mirtazapine[MeSH Terms]) AND (cancer[MeSH Terms])	67

Cochrane Library

search	**Query**	**Results**
#1	MeSH descriptor: [Depressive Disorder, Major] explode all trees	5 688
#2	MeSH descriptor: [Mirtazapine] explode all trees	328
#3	#1 AND #2	77
#4	#3 in Cochrane Reviews	1
#5	#2 in Cochrane Reviews	7

Appendix 3: Characteristics of included studies

Systematic reviews

Citation	PICO	Study design	Population (n)	Treatment	Main findings
Wanatabe et al. 2011[2]	1 & 2	Cochrane Systematic Review	29 RCTs, n=4974 Individuals aged 18 years or older, with depression.	Mirtazapine versus other antidepressants (tricyclics, selective serotonin reuptake inhibitors, serotonin-noradrenalin reuptake inhibitors). Any dose.	• Primary outcome for the review was reduction in depression severity at different time points. • Secondary outcomes related to PICO 1 and 2 extracted: **PICO 1: Cardiac related symptoms** - Fewer participants in the mirtazapine groups experienced hypertension or tachycardia than in the TCA groups (OR 0.44, 95% CI 0.24 to 0.81, P=0.01; i2=0%; 4 studies, n=552). No data was available for comparison of mirtazapine and SSRIs or SNRIs for this outcome. - Fewer participants in the mirtazapine groups experienced hypotension or bradycardia than in the TCA groups however the results were not significant (OR 0.46, 95% CI 0.12 to 1.81, P=0.86; i2=0%; 2 studies, n=215). Results were similar in the comparison of mirtazapine and SNRIs (OR 0.19 95% CI 0.02 to 1.68, P=0.14; 1 study, n=157). More participants in the mirtazapine groups experienced hypotension or bradycardia than in the SSRI groups however results were also not significant (OR 5.41, 95% CI 0.61 to 47.62, P=0.13; 1 studies, n=137). - More participants experienced dizziness, vertigo or faintness in the mirtazapine groups compared to the TCA groups, results were not significant (OR 3.04 95% CI 0.59 to 15.53, P = 0.18; i2=30.85%; 7 studies, n=1166). No difference was found in participants experiencing dizziness, vertigo or faintness between mirtazapine and SSRI groups (OR 1.04 95% CI 0.77 to 1.41, P = 0.79; i2=30.85%; 10 studies, n=2658). No data was availability for the comparison of mirtazapine and SNRIs. **PICO 2: Side-effects beneficial for some oncology patients** - No difference found between mirtazapine and TCA groups in participants experiencing weight gain or increased appetite (OR 1.04, 95% CI 0.58 to 1.86, P = 0.89; i2=29.05%; 3 studies, n=463). - More participants experienced sleep disturbance in the mirtazapine group compared to the TCA group however results were not reported to be significant (OR 1.43, 95% CI 0.69 to 2.98, P=0.34; 1 study, n=207).

Citation	PICO	Study design	Population (n)	Treatment	Main findings
					- No difference found between mirtazapine and TCA groups in participants experiencing sleepiness, drowsiness or somnolence (OR 0.92, 95% CI 0.66 to 1.27, P = 0.07; i2=70.57%; 6 studies, n=941).
Economos et.al. 2020[3]	PICO 2	Systematic Review – narratively synthesized	12 articles (2 RCTs, 3 non-randomised controlled trials and 7 non-randomised, non-controlled trials) 392 cancer patients with one or more of following symptoms: depression, anxiety, sleep disorders, nausea, anorexia, weight loss, etc.	Mirtazapine compared to other antidepressants as well as treatments such as antiemetics.	• Primary outcome – effectiveness of mirtazapine on multiple symptoms including depression • Individual symptoms - Weak evidence in effectiveness of weight gain, 4 studies, n=148; Graded as very low quality evidence. - Evidence to show that mirtazapine might be effective earlier than other antidepressants, 8 studies, 249, graded as very low quality evidence. - Weak evidence in effectiveness of improving appetite, 3 studies, n=113, graded as very low quality evidence.

Randomised trials

Citation	PICO	Study design	Population (n)	Treatment	Main findings
Carpenter et al, 2002	PICO 4	Randomised, double-blind, placebo-controlled study	Patients with persistent major depression despite adequate antidepressant monotherapy, n = 26	Mirtazapine augmentation for 4 weeks OR Placebo	• Categorical response (Composite: GGI improvement and reduction in HRSD-17) at end point was 64% for mirtazapine augmentation and 20% for placebo (p =0.043), with remission rates of 45.4% and 13.3% for mirtazapine and placebo respectively (p = 0.068).

Citation	PICO	Study design	Population (n)	Treatment	Main findings
Fang et.al. 2010	PICO 3	Double-blind randomised control trial	Individuals 18 years or older with major depressive disorder classified as treatment resistant (failed or inadequately responded to two or more antidepressants from different classes) n=150	Mirtazapine 45mg/day (n=55) vs Extended-release venlafaxine 225mg/day (n=50) vs Paroxetine 20mg/day (n=45)	• Primary outcome was remission rate at 8 weeks defined by the Hamilton Rating Scale for Depression 17-item (HRSD-17) total score of 7 or smaller. - There was a higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the venlafaxine-XR group compared to the mirtazapine group but results were not significant (mirtazapine n=20 (36.4%) vs venlafaxine-XR n=21 (42%); P=0.578). - Similarly, there was higher percentage of participants with a score of 7 or less on the HRSD-17 tool in the paroxetine group compared to the mirtazapine groups but results were not significant (mirtazapine n=20 (36.4%) vs paroxetine n=21 (46.7%); P=0.578).
Kato et al, 2017	PICO 4	Open label, randomised study	Patients with major depressive disorder (n = 154)	Step 1: Mirtazapine or SSRI for 4 weeks. Step 2: Non-responders: Mirtazapine or SSRI monotherapy or combination therapy for 4 weeks.	• Combination mirtazapine and SSRI showed significant improvement in HAM-D at week 6 (p = 0.006) and week 8 (p = 0.013).
Kessler D et.al. 2018	PICO 4	Multicentre, placebo-controlled randomised trial	Adults (≥ 18 years) with depression, taking SSRI or SNRI for at least 6 weeks at appropriate score with a BDI-II score ≥ 14 points. N =480 (431 followed up for full 12 weeks)	Mirtazapine (15mg daily initially increased to 30mg) plus usual care (SSRI or SNRI) Vs Usual care (SSRI or SNRI) plus Placebo	• After 12 weeks, the Beck Depression Inventory-II (BDI-II) scores (scale utilized and adjusted for base line score) were lower in mirtazapine group compared to the placebo group (difference – 1.83 points, 95% CI -3.92 to 0.27 points, p=0.087), not a significant difference, and not a clinically important difference). • At 24 weeks (difference 0.85 points, 95% CI -3.12 to 1.43 points) • At 12 months (difference 0.17 points, 95% CI -2.13 to 2.46)
Xiao et al. 2021	PICO 4	Double blind RCT	Individuals aged 18-60 years with major depressive disorder and early non-response to paroxetine (after two weeks in an open-label phase). (n=204)	Mirtazapine plus paroxetine (n=68) Vs Mirtazapine plus placebo (n=68) Vs Paroxetine plus placebo (n=68)	• Primary outcome improvement on the Hamilton Rating Scale for Depression 17-item (HRSD-17) scores after 6 weeks. • Small difference found in favour of mirtazapine plus paroxetine group compared to placebo groups however not significant (mean difference in change from baseline 0.77, 95% CI -1.86 to 3.39, P=0.6175). Significant differences were reported in HAMD-17 scores between groups at baseline however analyses conducted to explore impact did not alter the direction of the results.

Appendix 4: Excluded Studies

Citation	Reason for exclusion
Scott F, Hampsey E, Gnanapragasam S, Carter B, Marwood, Taylor RW, et.al. Systematic review and meta-analysis of augmentation and combination treatment for early-stage treatment-resistant depression. Journal of Psychopharmacology. 2023, 37(3): 268-278.	Two mirtazapine studies included, only one met PICO – thus only that particular study included
Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression. JAMA Psychiatry. 2022, 79(4):300-312.	Ten mirtazapine studies include, only 5 met PICO – these particular studies were included
Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2022 Mar 2;3(3):CD002795. doi: 10.1002/14651858.CD002795.pub3. PMID: 35234292; PMCID: PMC8889888.	Incorrect population
Salisbury-Afshar E. Adverse Events of Pharmacologic Treatments of Major Depression in Older Adults. Am Fam Physician. 2020 Feb 1;101(3):179-181. PMID: 32003957.	Clinical practice guidelines
Furukawa TA, Salanti G, Cowen PJ, Leucht S, Cipriani A. No benefit from flexible titration above minimum licensed dose in prescribing antidepressants for major depression: systematic review. Acta Psychiatr Scand. 2020 May;141(5):401-409. doi: 10.1111/acps.13145. Epub 2020 Jan 17. PMID: 31891415.	Study on flexible dosing
Noma H, Furukawa TA, Maruo K, Imai H, Shinohara K, Tanaka S, Ikeda K, Yamawaki S, Cipriani A. Exploratory analyses of effect modifiers in the antidepressant treatment of major depression: Individual-participant data meta-analysis of 2803 participants in seven placebo-controlled randomized trials. J Affect Disord. 2019 May 1;250:419-424. doi: 10.1016/j.jad.2019.03.031. Epub 2019 Mar 6. PMID: 30878654.	Study on treatment modifiers
Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. Cochrane Database Syst Rev. 2018 Aug 6;8(8):CD012708. doi: 10.1002/14651858.CD012708.pub2. PMID: 30080242; PMCID: PMC6513659.	Incorrect population
Zheng W, Zhang YF, Zhong HQ, Mai SM, Yang XH, Xiang YT. Wuling Capsule for Major Depressive Disorder: A Meta-analysis of Randomised Controlled Trials. East Asian Arch Psychiatry. 2016 Sep;26(3):87-97. PMID: 27703096.	Incorrect intervention
Thase ME, Nierenberg AA, Vrijland P, van Oers HJ, Schutte AJ, Simmons JH. Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. Int Clin Psychopharmacol. 2010 Jul;25(4):189-98. doi: 10.1097/YIC.0b013e328330adb2. PMID: 20531012.	Later systematic review (Watanabe et al. 2011 - Cochrane) chosen for inclusion
Bech P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. Int J Neuropsychopharmacol. 2001 Dec;4(4):337-45. doi: 10.1017/S1461145701002565. PMID: 11806859.	
Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. J Clin Psychiatry. 1998 Mar;59(3):123-7. PMID: 9541155.	
Kasper S, Zivkov M, Roes KC, Pols AG. Pharmacological treatment of severely depressed patients: a meta-analysis comparing efficacy of mirtazapine and amitriptyline. Eur Neuropsychopharmacol. 1997 May;7(2):115-24. doi: 10.1016/s0924-977x(96)00394-x. PMID: 9169299.	
Stahl S, Zivkov M, Reimitz PE, Panagides J, Hoff W. Meta-analysis of randomized, double-blind, placebo-controlled, efficacy and safety studies of mirtazapine versus amitriptyline in major depression. Acta Psychiatr Scand Suppl. 1997;391:22-30. doi: 10.1111/j.1600-0447.1997.tb05955.x. PMID: 9265948.	
Lopes Rocha F, Fuzikawa C, Riera R, Ramos MG, Hara C. Antidepressant combination for major depression in incomplete responders--a systematic review. J Affect Disord. 2013 Jan 10;144(1-2):1-6. doi: 10.1016/j.jad.2012.04.048. Epub 2012 Jul 24. PMID: 22835845.	Cochrane review (Watanabe et al. 2011)

Egberts AC, Lenderink AW, de Koning FH, Leufkens HG. Channeling of three newly introduced antidepressants to patients not responding satisfactorily to previous treatment. J Clin Psychopharmacol. 1997 Jun;17(3):149-55. doi: 10.1097/00004714-199706000-00002. PMID: 9169957.	Incorrect study design – retrospective chart review
Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol Psychiatry. 2008 Apr 1;63(7):699-704. doi: 10.1016/j.biopsych.2007.08.010. Epub 2007 Oct 24. PMID: 17919460.	Incorrect intervention
Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, Hawley C, Kasper S, Linden M, Massana J, Mendlewicz J, Möller HJ, Nemeroff CB, Saiz J, Such P, Torta R, Versiani M. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. J Clin Psychiatry. 2002 Sep;63(9):826-37. doi: 10.4088/jcp.v63n0913. PMID: 12363125.	Guidelines
Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry. 2002 Jan 15;51(2):183-8. doi: 10.1016/s0006-3223(01)01262-8. PMID: 11822997.	Included in Lopes Rocha systematic review
Fava M, Dunner DL, Greist JH, Preskorn SH, Trivedi MH, Zajecka J, Cohen M. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry. 2001 Jun;62(6):413-20. doi: 10.4088/jcp.v62n0603. PMID: 11465517.	Included in Lopes Rocha systematic review
Blier P, Gobbi G, Turcotte JE, de Montigny C, Boucher N, Hébert C, Debonnel G. Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. Eur Neuropsychopharmacol. 2009 Jul;19(7):457-65. doi: 10.1016/j.euroneuro.2009.01.015. Epub 2009 Apr 2. PMID: 19345072.	Incorrect population
Cankurtaran ES, Ozalp E, Soygur H, Akbiyik DI, Turhan L, Alkis N. Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine. Support Care Cancer. 2008 Nov;16(11):1291-8. doi: 10.1007/s00520-008-0425-1. Epub 2008 Feb 26. PMID: 18299900.	Included in Economos et al. 2020 systematic review
Davis MP, Kirkova J, Lagman R, Walsh D, Karafa M. Intolerance to mirtazapine in advanced cancer. J Pain Symptom Manage. 2011 Sep;42(3):e4-7. doi: 10.1016/j.jpainsymman.2011.05.002. PMID: 21854992.	
Ersoy MA, Noyan AM, Elbi H. An open-label long-term naturalistic study of mirtazapine treatment for depression in cancer patients. Clin Drug Investig. 2008;28(2):113-20. doi: 10.2165/00044011-200828020-00005. PMID: 18211119.	
Kim SW, Shin IS, Kim JM, Kim YC, Kim KS, Kim KM, Yang SJ, Yoon JS. Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression. Psychiatry Clin Neurosci. 2008 Feb;62(1):75-83. doi: 10.1111/j.1440-1819.2007.01778.x. PMID: 18289144.	
Ozsoy S, Besirli A, Unal D, Abdulrezzak U, Orhan O. The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy. Gen Hosp Psychiatry. 2015 Jan-Feb;37(1):31-5. doi: 10.1016/j.genhosppsych.2014.09.002. Epub 2014 Sep 6. PMID: 25440723.	
Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, McGuire H, Churchill R, Furukawa TA; MANGA (Meta-Analysis of New Generation Antidepressants) Study Group. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute-phase treatment of adults with depression: systematic review and meta-analysis. CNS Drugs. 2010 Jan;24(1):35-53. doi: 10.2165/11319480-000000000-00000. PMID: 20030418.	Included updated Cochrane review instead
Henssler J, Bschor T, Baethge C. Combining Antidepressants in Acute Treatment of Depression: A Meta-Analysis of 38 Studies Including 4511 Patients. Can J Psychiatry. 2016 Jan;61(1):29-43. doi: 10.1177/0706743715620411. Epub 2016 Jan 1. PMID: 27582451; PMCID: PMC4756602.	Incorrect population
Honig A, Kuyper AM, Schene AH, van Melle JP, de Jonge P, Tulner DM, Schins A, Crijns HJ, Kuijpers PM, Vossen H, Lousberg R, Ormel J; MIND-IT investigators. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. Psychosom Med. 2007 Sep-Oct;69(7):606-13. doi: 10.1097/PSY.0b013e31814b260d. Epub 2007 Sep 10. PMID: 17846258.	Incorrect comparator
Dragioti E, Solmi M, Favaro A, Fusar-Poli P, Dazzan P, Thompson T, Stubbs B, Firth J, Fornaro M, Tsartsalis D, Carvalho AF, Vieta E, McGuire P, Young AH, Shin JI, Correll CU, Evangelou E. Association of Antidepressant Use With Adverse Health Outcomes: A Systematic Umbrella Review. JAMA Psychiatry. 2019 Dec 1;76(12):1241-1255. doi: 10.1001/jamapsychiatry.2019.2859. Erratum in: JAMA Psychiatry. 2021 May 1;78(5):569. PMID: 31577342; PMCID: PMC6777224.	Focused on antidepressant use in general – wrong intervention
Na KS, Jung HY, Cho SJ, Cho SE. Can we recommend mirtazapine and bupropion for patients at risk for bleeding?: A systematic review and meta-analysis. J Affect Disord. 2018 Jan 1;225:221-226. doi: 10.1016/j.jad.2017.08.002. Epub 2017 Aug 8. PMID: 28841484.	Incorrect comparator

Hunter CN, Abdel-Aal HH, Elsherief WA, Farag DE, Riad NM, Alsirafy SA. Mirtazapine in Cancer-Associated Anorexia and Cachexia: A Double-Blind Placebo-Controlled Randomized Trial. J Pain Symptom Manage. 2021 Dec;62(6):1207-1215. doi: 10.1016/j.jpainsymman.2021.05.017. Epub 2021 May 26. PMID: 34051293.	Incorrect comparator
Allen ND, Leung JG, Palmer BA. Mirtazapine's effect on the QT interval in medically hospitalized patients. Ment Health Clin. 2020 Jan 9;10(1):30-33. doi: 10.9740/mhc.2020.01.030. PMID: 31942276; PMCID: PMC6956977.	Incorrect study design

Appendix 5: AMSTAR 2 Checklist

Watanabe et al. 2011 Cochrane Systematic 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?	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 Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
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**	Partial Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	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

Economos et al. 2020 Cochrane Systematic 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 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 Yes
5. Did the review authors perform study selection in duplicate?	No
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 exclusions?	Yes

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

Appendix 6: Forest plots – Watanabe et al. 2011 Cochrane review

Figure 1: Forest plot comparison Mirtazapine vs TCA – No. experiencing hypertension or tachycardia

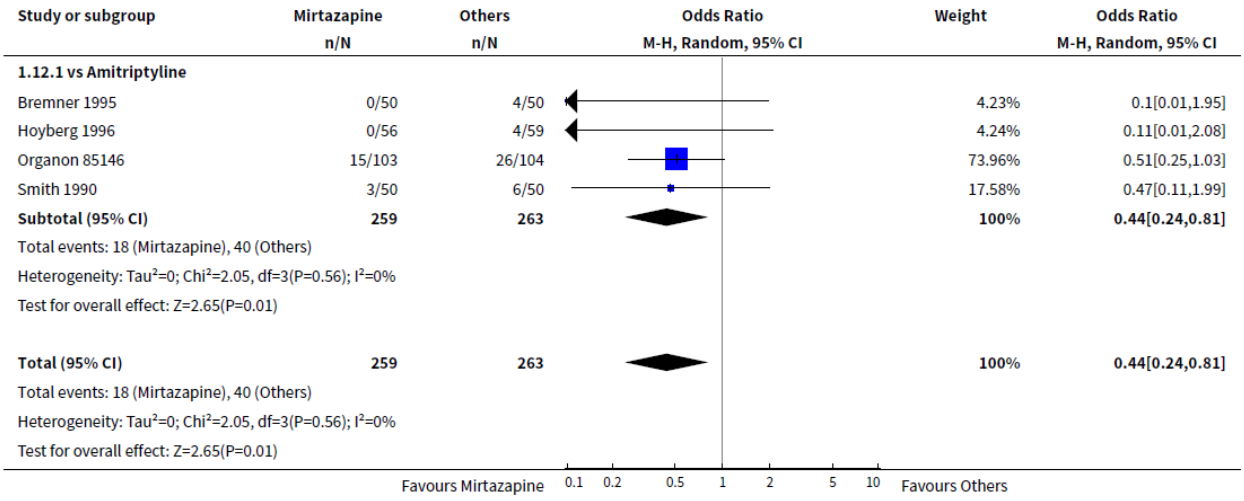


Figure 2. Forest plot of comparison Mirtazapine vs TCA – No. experiencing hypotension or bradycardia

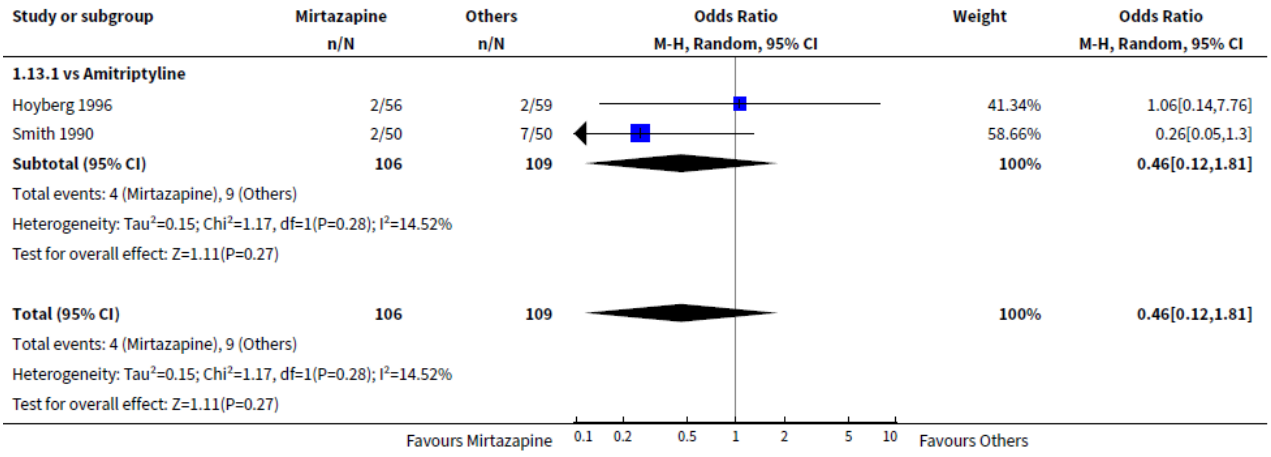


Figure 3. Forest plot of comparison Mirtazapine vs TCA – No. experiencing dizziness, vertigo or faintness

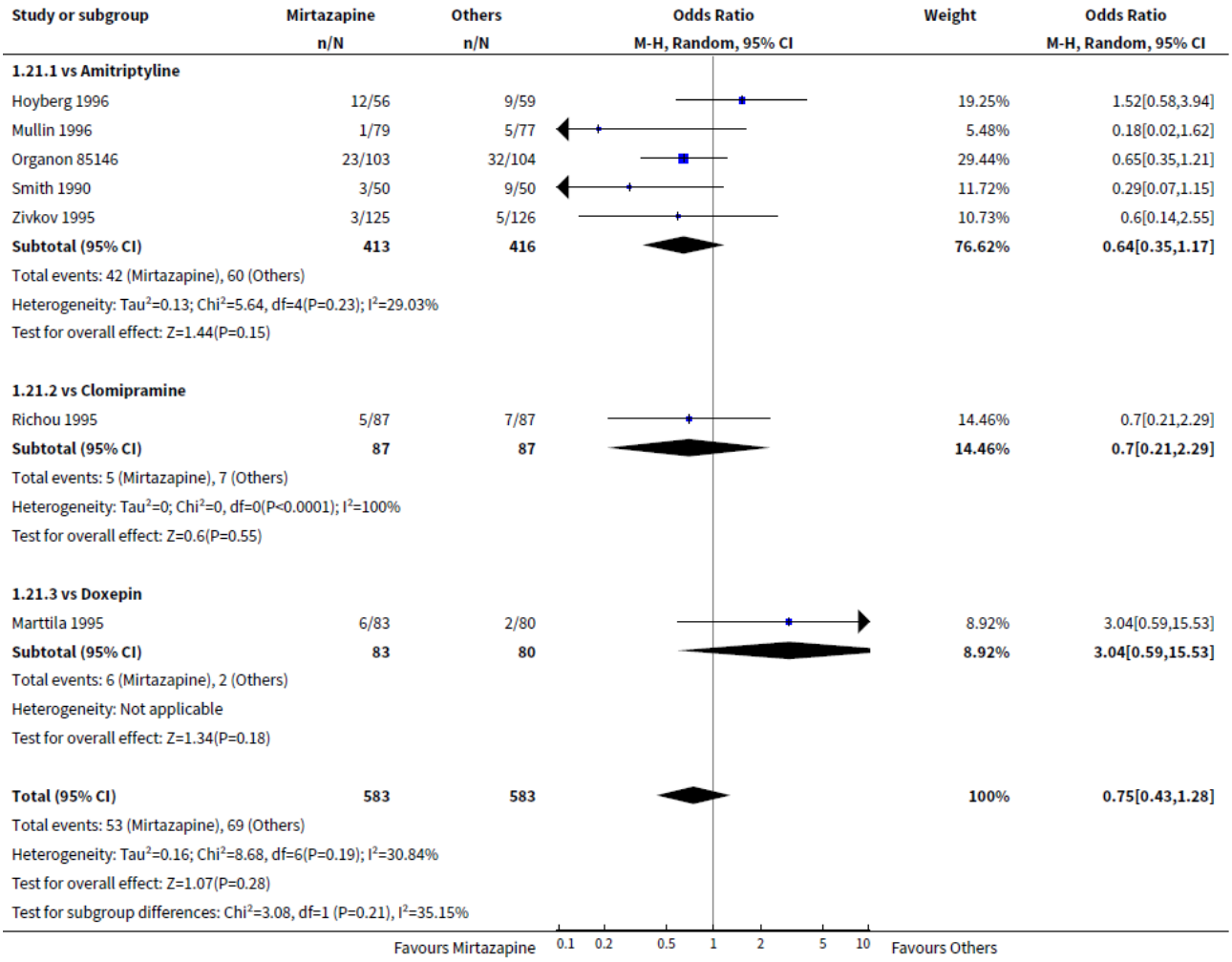


Figure 4. Forest plot of comparison Mirtazapine vs SSRIs – No. experiencing hypotension or bradycardia

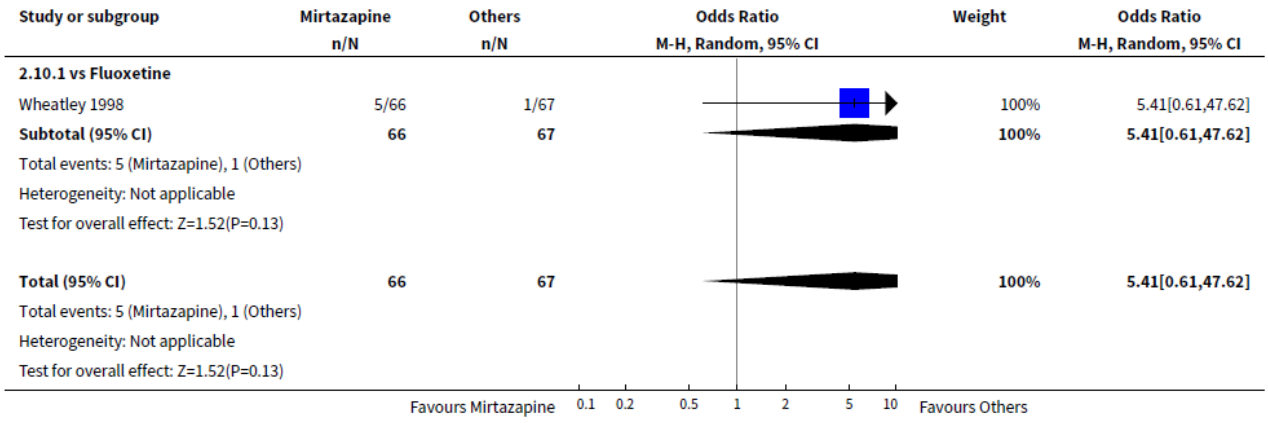


Figure 5. Forest plot of comparison Mirtazapine vs SSRIs – No. experiencing dizziness, vertigo or faintness

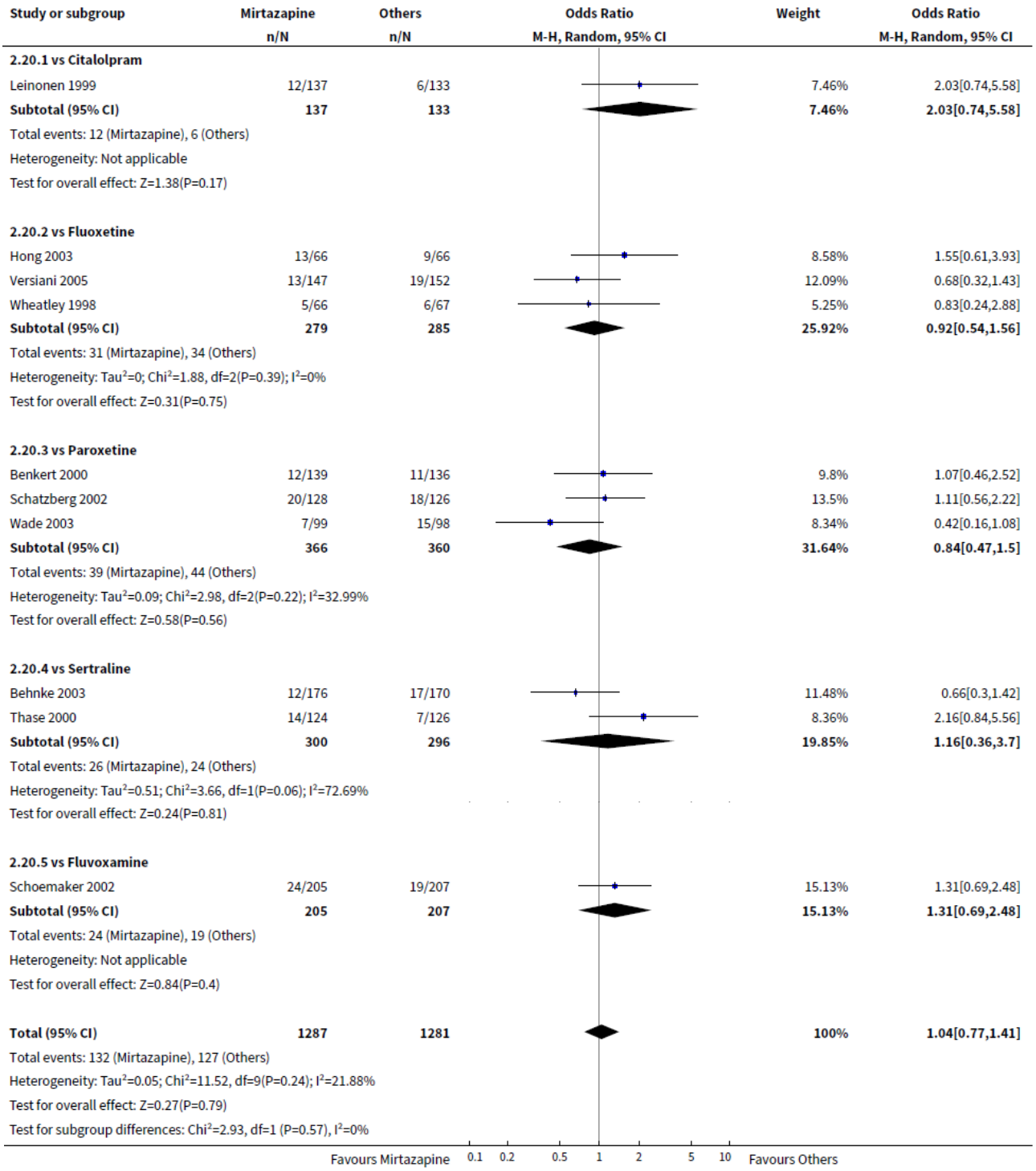

Study or subgroup
Mirtazapine n/N
Others n/N
Odds Ratio M-H, Random, 95% CI
Weight
Odds Ratio M-H, Random, 95% CI
2.20.1 vs Citalolpram
Leinonen 1999 12/137 6/133 7.46% 2.03[0.74,5.58]
Subtotal (95% CI) 137 133 7.46% 2.03[0.74,5.58]
Total events: 12 (Mirtazapine), 6 (Others)
Heterogeneity: Not applicable
Test for overall effect: Z=1.38(P=0.17)
2.20.2 vs Fluoxetine
Hong 2003 13/66 9/66 8.58% 1.55[0.61,3.93]
Versiani 2005 13/147 19/152 12.09% 0.68[0.32,1.43]
Wheatley 1998 5/66 6/67 5.25% 0.83[0.24,2.88]
Subtotal (95% CI) 279 285 25.92% 0.92[0.54,1.56]
Total events: 31 (Mirtazapine), 34 (Others)
Heterogeneity: Tau²=0; Chi²=1.88, df=2(P=0.39); I²=0%
Test for overall effect: Z=0.31(P=0.75)
2.20.3 vs Paroxetine
Benkert 2000 12/139 11/136 9.8% 1.07[0.46,2.52]
Schatzberg 2002 20/128 18/126 13.5% 1.11[0.56,2.22]
Wade 2003 7/99 15/98 8.34% 0.42[0.16,1.08]
Subtotal (95% CI) 366 360 31.64% 0.84[0.47,1.5]
Total events: 39 (Mirtazapine), 44 (Others)
Heterogeneity: Tau²=0.09; Chi²=2.98, df=2(P=0.22); I²=32.99%
Test for overall effect: Z=0.58(P=0.56)
2.20.4 vs Sertraline
Behnke 2003 12/176 17/170 11.48% 0.66[0.3,1.42]
Thase 2000 14/124 7/126 8.36% 2.16[0.84,5.56]
Subtotal (95% CI) 300 296 19.85% 1.16[0.36,3.7]
Total events: 26 (Mirtazapine), 24 (Others)
Heterogeneity: Tau²=0.51; Chi²=3.66, df=1(P=0.06); I²=72.69%
Test for overall effect: Z=0.24(P=0.81)
2.20.5 vs Fluvoxamine
Schoemaker 2002 24/205 19/207 15.13% 1.31[0.69,2.48]
Subtotal (95% CI) 205 207 15.13% 1.31[0.69,2.48]
Total events: 24 (Mirtazapine), 19 (Others)
Heterogeneity: Not applicable
Test for overall effect: Z=0.84(P=0.4)
Total (95% CI) 1287 1281 100% 1.04[0.77,1.41]
Total events: 132 (Mirtazapine), 127 (Others)
Heterogeneity: Tau²=0.05; Chi²=11.52, df=9(P=0.24); I²=21.88%
Test for overall effect: Z=0.27(P=0.79)
Test for subgroup differences: Chi²=2.93, df=1 (P=0.57), I²=0%
Favours Mirtazapine
0.1
0.2
0.5
1
2
5
10
Favours Others

Figure 6. Forest plot of comparison Mirtazapine vs SNRIs – No. experiencing hypotension or bradycardia

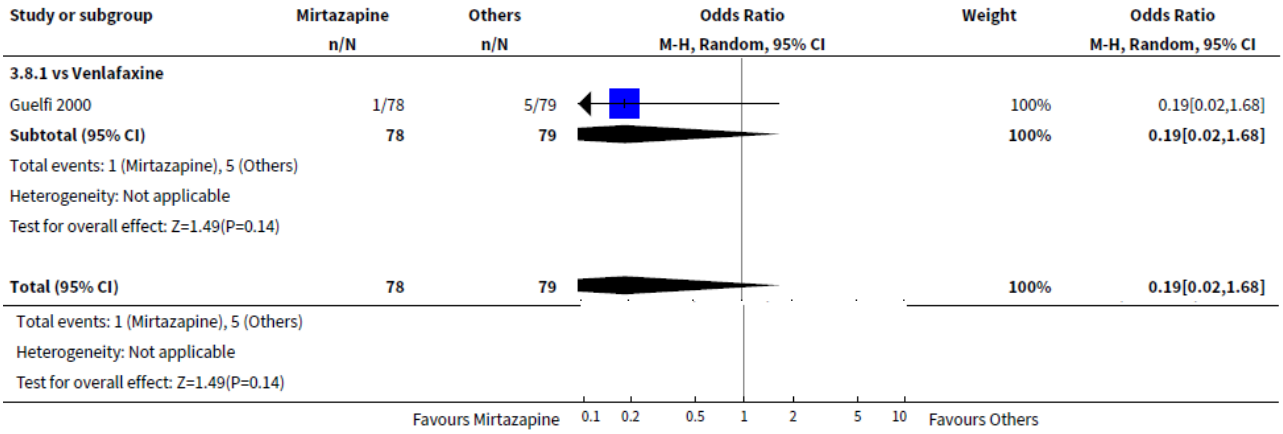
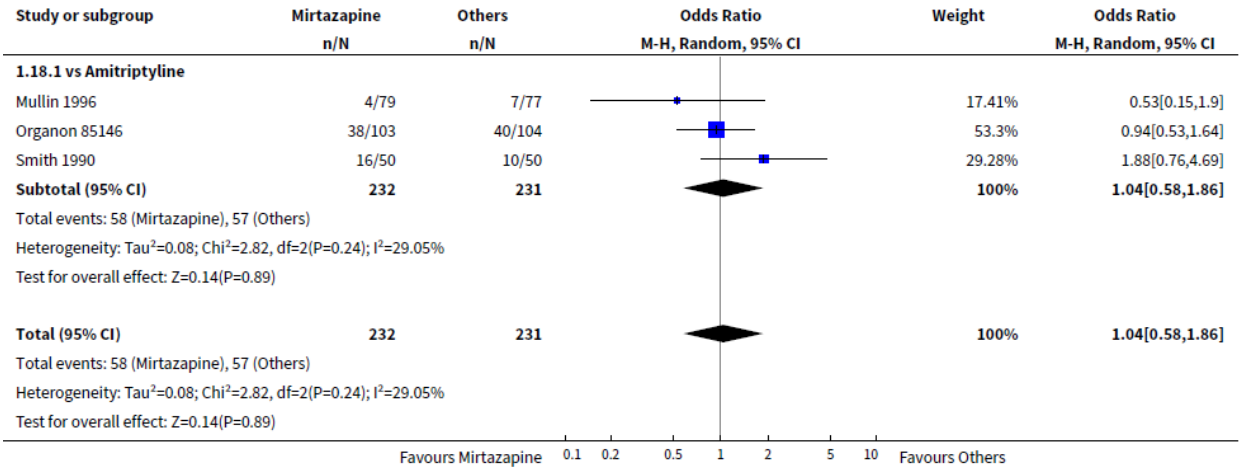


Figure 7. Forest plot of comparison Mirtazapine vs TCA – No. experiencing weight gain or increased appetite



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