Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with agitated depression (or severe agitated or anxious features comorbid to depression), which intervention is most effective, compared to treatment as usual, in reducing symptoms of agitation and depression?

Clarification of question using PICO structure

Patients: Adults with agitated depression or severe agitated or anxious features comorbid to depression.
Intervention: Any intervention
Comparator: Treatment as usual
Outcome: Reduction in symptoms of agitation and depression.

Clinical and research implications

Evidence from a meta-analysis of eight randomised controlled trials (RCTs) indicated that mirtazapine is superior to placebo and similar to amitriptyline for reducing symptoms of anxiety in people with moderate to severe depression. Two additional RCTs provided data indicating that the selective serotonin reuptake inhibitors fluoxetine, sertraline, and paroxetine are similarly effective in treating people with major depression and anxiety and that fluoxetine is similarly effective to amitriptyline; the majority of participants in both of these trails had experienced recurrent episodes of major depression. All studies in this evidence summary reported results which indicated improvements in symptoms of anxiety following treatment with antidepressant medication. These results are likely to be reliable, but further RCTs would be useful to explore the effectiveness of other pharmacological and non-pharmacological therapeutic options.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one meta-analysis of eight RCTs, which compared mirtazapine with placebo or amitriptyline; studies included in this analysis did not appear to have been derived from a systematic review.[1] Two additional RCTs were identified, one which compared the effectiveness and tolerability of three SSRIs, fluoxetine, sertraline, and paroxetine,[2] and one which compared fluoxetine with amitriptyline.[3] All studies included only participants with moderate to severe depression and symptoms of anxiety, based on components of the Hamilton Rating Scale for Depression (HAM-D).[1,2,3] The majority of participants in the two single RCTs had experienced recurrent episodes of major depression.[2,3] All studies reported data on the effectiveness of treatments in reducing symptoms of anxiety, based on HAM-D scores.[1,2,3]

Main Findings

The meta-analysis of eight RCTs found that mirtazapine was effective in reducing symptoms of anxiety when compared to placebo.[1] A comparison of improvements, from baseline to week six of treatments, showed that participants in the mirtazapine group experienced greater reductions in anxiety/agitation (mean change from baseline 3.2±0.2 versus 1.9±0.2, $p \leq 0.05$) and greater reductions in anxiety/somatisation (mean change from baseline 0.45±0.2 versus 0.36±0.2, $p \leq 0.03$) than those in the placebo group.[1] There were no statistically significant differences in effectiveness between mirtazapine and amitriptyline.[1] The two remaining studies were both comparisons of active treatments with no placebo control group, although both attempted to control for placebo effect by including a placebo run-in phase.[2,3] One trial showed that the three SSRIs fluoxetine, sertraline, and paroxetine were similarly effective in treating patients with severe depression and anxiety. Overall, 70% of patients achieved a response, defined as a 50% or greater decrease in HAM-D-17 total score from baseline to endpoint, (fluoxetine, 73%; sertraline, 86%; paroxetine, 77%) and 50% of patients achieved a remission, defined as a total HAM-D-17 score ≤7 at endpoint (fluoxetine, 53%; sertraline, 62%; paroxetine, 50%).[2] The remaining trial showed that fluoxitine and amitriptyline were similarly effective in reducing symptoms of anxiety; the rate of improvement, defined as at least a 50% reduction in anxiety-agitation factor score between baseline and end of treatment, was 87% in the amitriptyline group and 85% in the fluoxetine group.[3]

Authors Conclusions

A meta-analysis of eight RCTs concluded that mirtazapine was more effective than placebo and comparable to amitriptyline in reducing symptoms of anxiety/agitation or anxiety/somatisation in patients with major depression. The remaining two RCTs included in this evidence summary concluded that the SSRIs fluoxetine, sertraline, and paroxetine had similar efficacy and tolerability, and that fluoxetine was comparable to amitriptyline for the treatment of patients with high levels of baseline anxiety symptoms during the acute treatment of major depression.

Reliability of conclusions/Strength of evidence

One meta-analysis, which included eight RCTs with approximately 1000 participants in total, provided good quality evidence that mirtazapine is superior to placebo and similar to amitriptyline for reducing symptoms of anxiety in people with moderate to severe depression.[1] It should be noted that the risk of bias table below does not reflect the true methodological quality of this study, as the rating tool used was designed for systematic reviews not meta-analyses alone.[1] Two single RCTs of

moderate methodological quality, with some weaknesses in reporting, provided data indicating that the SSRIs fluoxetine, sertraline, and paroxetine are similarly effective in treating people with major depression and anxiety,[2] and that fluoxetine is similarly effective to amitriptyline.[3] These results are likely to be reliable, but further RCTs would be useful to explore the effectiveness of other pharmacological and non-pharmacological therapeutic options.

What do guidelines say?

Very little was found in clinical guidelines for treating agitated depression. The following was found in NICE (2009) regarding agitation and anxiety as a result of antidepressant medication;

(Page 17)
Advise people with depression of the potential for increased agitation, anxiety and suicidal ideation in the initial stages of treatment; actively seek out these symptoms and:

- ensure that the person knows how to seek help promptly
- review the person's treatment if they develop marked and/or prolonged agitation.

(Page 25)
If a person with depression develops side effects early in antidepressant treatment, provide appropriate information and consider one of the following strategies:

- in discussion with the person, consider short-term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (except in people with chronic symptoms of anxiety); this should usually be for no longer than 2 weeks in order to prevent the development of dependence.

The evidence presented in this summary does not contradict current guidance.

Date question received: 18/07/2013
Date searches conducted: 31/07/2013
Date answer completed: 10/09/2013

References

RCTs

1. Fawcett, J. and Barkin, R.L. (1998) 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. *Journal of Clinical Psychiatry 59* (**3**). Pp. 123-127.

2. Fava, M., Rosenbaum, J.F., Hoog, S.L., Tepner, R.G., Kopp, J.B. and Nilsson, M.E. (2000) Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. *Journal of Affective Disorders (59)* pp. 119-126.

3. Marchesi, C., Ceccherininelli, A., Rossi, A. and Maggini, C. (1998) Is Anxious-Agitated Major Depression Respomsible to Fluoxetine? A Double-Blind Comparison with Amitriptyline. *Pharmacopsychiat. 31*. Pp.216-221.

Guidelines

4. National Institute for Health and Care Excellence (2009) Depression in adults. The treatment and management of depression in adults. CG90. London: National Institute for Health and Care Excellence.
   http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Fawcett (1998)	Unknown	*Population*: The article did not specify any inclusion criteria in relation to study participants; the characteristics of the participants of studies included in the met-analysis are described in the results column. *Intervention*: Mirtazapine *Comparator*: The article did not specify any inclusion criteria with respect to comparators; all included studies had a placebo arm and four of the eight included studies also included an active comparator arm (amitriptyline). *Outcomes*: Change in anxiety/agitation or anxiety/somatisation levels, as measured by selected items on the HAM-D scale. *Study design*: Randomised controlled trials (RCTs) conducted in the U.S.A.	8 (total n = 978)	This study aimed to assess the effects of mirtazapine on the symptoms of anxiety/agitation or anxiety/somatisation Hamilton Rating Scale for Depression (HAM-D factor score I) associated with depression. Studies included in the review were of moderately to severely depressed patients with total baseline HAM-D scores ≥18 for the first 17 items on the 21 item HAM-D and a score of ≥6 for the HAM-D anxiety/agitation factor. Participants had a mean age of 43 years (range 18 to 92) and 57% of the total population were female. Studies excluded participants with a history of schizophrenia or other psychotic disorder, atypical depression, drug or alcohol abuse, attempted overdose, attempted suicide, concomitant use of other psychotropic medication, significant medical illness, breast feeding mothers within six months post-partum, and participants who had received electroconvulsive therapy within	The article reported a met-analysis and it did not appear that this was based on a systematic review. The research question did not specify any inclusion criteria with respect to the population characteristics or comparator interventions. No literature searches were described; the article stated only that it reported a meta-analysis of

				the previous three months. Included studies compared treatment with mirtazapine to treatment with amitriptyline or placebo. Included studies used a fixed dose (5-35mg) daily, or flexible doses (5-60mg) daily of mirtazapine. Participants in the amitriptyline arms of included studies received a daily dose of 40-280mg. Mirtazapine versus placebo: 161 Patients in the mirtazapine group and 132 patients in the placebo group met the criteria for high baseline levels of anxiety and were included in the outcome analysis for HAM-D anxiety/agitation scores. Patients in the mirtazapine treated group experienced a significantly greater improvement (baseline to week 6) than those in the placebo group; mean change from baseline 3.2±0.2 versus 1.9±0.2, p≤0.05. Similar results were noted for the anxiety/somatisation analysis, which included all study participants (n=791). The mean change from baseline to week 6, in HAM-D Factor Score I was 0.45±0.2 in the mirtazapine-treated patients versus 0.36±0.2 in the placebo group, p≤0.03. Mirtazipne versus amytriptyline:	eight RCTs. No review process, or quality assessment of included studies, was reported; this article appears to report a meta-analysis of RCTs, **not** a systematic review which includes meta-analysis. Meta-analysis appears to have been conducted, using individual patient data from included studies, on an intention-to-treat basis.

				Both active treatment groups showed significant reductions in symptoms of anxiety/agitation and anxiety/somatisation, from baseline to week six; there were no significant differences in treatment effect between the two groups.	

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Fava (2000)	*Participants*: Outpatients meeting the criteria for major depression or atypical major depression, according to DSM-IV, were eligible for inclusion if they scored 16 or higher on the first 17 items of the 28 item HAM-D-28. Exclusion criteria: pregnancy or lactation; concomitant physical illness; other psychiatric diagnoses (e.g. schizophrenia, bipolar disorder, personality disorders, substance abuse, etc.); a history of allergies to psychiatric medication; concomitant use of non-study antidepressants, anxiolytics, or other psychotropic medication. *Intervantion*: Fluoxetine, daily dose of 20mg. *Comparator*: Sertraline daily dose of 50 mg or Paroxetine, daily dose of 20mg.	n=108 (fluoxetine n= 35, sertraline n =43 paroxetine n=30)	This study aimed to compare the efficacy and tolerability of different selective serotonin reuptake inhibitors (SSRIs) in patients with anxious depression. Treatment groups were comparable at baseline with respect to age and gender, baseline HAM-D Total score and baseline HAM-D-Anxiety/ Somatisation Factor score. The mean age of study participants was approximately 42 years, approximately 65% were female and 69% had experienced a previous episode of major depression. Treatment effects were similar across the three SSRIs. There were no significant differences in baseline to endpoint improvement in HAM-D-17 total or HAM-D anxiety/somatisation factor score. Individual HAM-D items also showed no significant differences between treatments. 70% of patients achieved a response, defined as a 50% or greater decrease in HAM-D-17 total score from baseline to endpoint, (fluoxetine, 73%; sertraline, 86%; paroxetine, 77%; overall *P*=0.405) and 50% of patients	The article reports an RCT with a single-blind placebo lead-in phase "to eliminate placebo responders," followed by a double-blind treatment phase. No description of the randomisation process of allocation concealment was provided. It was not clear whether study outcomes were

	Outcomes: Change in anxiety, measured by HAM-D-17 and HAM-D Anxiety/ Somatization Factor score. Tolerability, measured by discontinuation of treatment or emergence of adverse events.		achieved a remission, defined as a total HAM-D-17 score ≤7 at endpoint (fluoxetine, 53%; sertraline, 62%; paroxetine, 50%; overall *P*=0.588). There were no statistically significant differences between the treatments in discontinuations or emergence of adverse events suggestive of agitation or sedation.	assessed independently/blind to treatment group. All study participants appear to have been included in the analyses and data were reported for all specified outcome measures.
Marchesi (1998)	*Participants*: Adult males and females. Selected from depressed patients (DSM-III-R) admitted to Italian psychiatric outpatient clinics. Patients were eligible if they had a total score on the Hamilton Rating Scale for Depression-17 items (HRSD) higher than 16 and the sum of the scored of the items 'agitation', 'psychic anxiety' and 'somatic anxiety' was higher than 5 or the score on at least 1 was higher than 3. Exclusion criteria: serious suicide risk; diagnosis of schizophrenia, epilepsy or organic brain disease; concomitant serious medical conditions; treated with antidepressants the week before enrolment. *Intervention*: Fluoxetine, daily dose of 20mg.	n = 142 (amitriptyline n=75m fluoxetine n=67).	This study aimed to compare the efficacy and safety of fluoxetine with that of amitriptyline for the treatment of anxious-agitated major depression. Participants in the two treatment groups were similar at baseline, with respect to age, gender, socioeconomic factors, baseline HRSD total score, and baseline HRSD anxiety-agitation score. The mean age of study participants was approximately 43 years and 74% were female. Approximately 73% of study participants had experienced recurrent episodes of major depression; it was not clear whether participants with recurrent depression were evenly distributed between the two treatment groups. Outcomes were measured at 1, 3, 6, and 10 weeks after the start of treatment. Both treatment groups showed a reduction in HRSD total	The article reports an RCT with a single-blind placebo lead-in phase, followed by a double-blind treatment phase. No description of the randomisation process of allocation concealment was provided. It was not clear whether study outcomes were assessed

	Comparator: Amitriptyline, daily dose initiated at 25mg then increased to 75mg at the end of the first week. *Outcomes*: Change in anxiety or agitation, according to HRSD, State Trait Anxiety Inventory (STAI) and the Covi Anxiety Scale (CAS). Hostility assessed with the Bass Durkee Questionnaire (QTA).		and HRSD anxiety-agitation scores, from baseline to the end of the study. Mean final scores were reported, but not change from baseline data. There were no statistically significant differences in change in HRSD total or HRSD anxiety-agitation between the two treatment groups, at the end of the study. The rate of improvement, defined as at least a 50% reduction in anxiety-agitation factor score between baseline and end of treatment, was similar in the two groups (amitriptyline 87% and fluoxetine 85%). Transient differences between the treatment groups were observed on various single items or the HRSD score at various time points during the study. There were no significant differences on other rating scales (STAI, CAS, or QTA) between the two treatment groups.	independently/blind to treatment group. All randomised patients, with at least one post-baseline measurement were included in the intention-to-treat analysis (last observation carried forward for dropouts). Full data were not reported for any outcome measure. Change form baseline data were only reported for time points where there was a significant difference between the treatment groups.

Risk of Bias: Systematic Reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Fawcett (1998)	☹	☹	☹	☹	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Fava (2000)	?	?	☺	?	☺	☺
Marchesi (1998)	?	?	☺	?	☺	☹

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Depression	464	1
DARE	1 (depress*) IN DARE 1829 Delete 2 MeSH DESCRIPTOR Depression EXPLODE ALL TREES 432 Delete 3 MeSH DESCRIPTOR Depressive Disorder EXPLODE ALL TREES 812 Delete 4 MeSH DESCRIPTOR Depressive Disorder, Major EXPLODE ALL TREES 254 Delete 5 (ECT) IN DARE 32 Delete 6 (electroconvulsive*) IN DARE 56 Delete 7 (electro* AND acupuncture*) IN DARE 142 Delete 8 (*deep* and *brain*) IN DARE 35 Delete 9 MeSH DESCRIPTOR Electroacupuncture EXPLODE ALL TREES 17 Delete 10 MeSH DESCRIPTOR Electroconvulsive Therapy EXPLODE ALL TREES 40 Delete 11 #1 OR #2 OR #3 OR #4 2222 Delete 12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 252 Delete 13 #11 AND #12		
Primary studies			
CENTRAL	agitated depression""agitated depression" 17 #2 Enter terms for search "severe depression""severe depression" 483 #3 Enter terms for search restlessnessrestlessness 727 #4 Enter terms for search agitationagitation 1645 #5 Enter terms for search anxietyanxiety 19351 #6 MeSH descriptor: [Psychomotor Agitation] this term only 400 #7 Enter terms for search #1 or #2 or #3 or #4 or #5 or #6#1 or #2 or #3 or #4 or #5 or #6 21200	59	

	#8 Enter terms for search ect or "electroconvulsive therapy"ect or "electroconvulsive therapy" 1091 #9 MeSH descriptor: [Electroconvulsive Therapy] this term only 477 #10Enter terms for searc#8 or #91091 #11Enter terms for searc#7 and #10 152 Central only 59		
PsycINFO	1. PsycINFO; "agitated depression".ti,ab; 150 results. 2. PsycINFO; (agitated adj3 depression).ti,ab; 187 results. 3. PsycINFO; exp MAJOR DEPRESSION/; 86711 results. 4. PsycINFO; AGITATION/ OR ANXIETY [+NT]/ OR RESTLESSNESS/; 42760 results. 5. PsycINFO; 2 OR 3 OR 4; 123202 results. 6. PsycINFO; ELECTROCONVULSIVE SHOCK THERAPY/; 4942 results. 7. PsycINFO; ECT.ti,ab; 5565 results. 8. PsycINFO; 6 OR 7; 6297 results. 9. PsycINFO; 5 AND 8; 2321 results. 10. PsycINFO; CLINICAL TRIALS/; 6862 results. 11. PsycINFO; random*.ti,ab; 120389 results. 12. PsycINFO; groups.ti,ab; 347570 results. 13. PsycINFO; (double adj3 blind).ti,ab; 17047 results. 14. PsycINFO; (single adj3 blind).ti,ab; 1305 results. 15. PsycINFO; EXPERIMENTAL DESIGN/; 8692 results. 16. PsycINFO; controlled.ti,ab; 75064 results. 17. PsycINFO; (clinical adj3 study).ti,ab; 7420 results. 18. PsycINFO; trial.ti,ab; 63403 results. 19. PsycINFO; "treatment outcome clinical trial".md; 24336 results. 20. PsycINFO; 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 536060 results. 21. PsycINFO; 9 AND 20; 545 results.	545	
Embase	14. EMBASE; "agitated adj3 depression".ti,ab; 0 results. 15. EMBASE; DEPRESSIVE DISORDER, MAJOR/; 33062 results.	326	

	16. EMBASE; "agitated depression".ti,ab; 138 results. 17. EMBASE; ANXIETY/; 106374 results. 18. EMBASE; agitat*.ti,ab; 17362 results. 19. EMBASE; PSYCHOMOTOR AGITATION/; 7762 results. 20. EMBASE; restless*.ti,ab; 8023 results. 21. EMBASE; 17 OR 18 OR 19 OR 20; 134062 results. 22. EMBASE; 15 OR 16 OR 21; 164220 results. 23. EMBASE; ELECTROCONVULSIVE THERAPY/; 15060 results. 24. EMBASE; (ECT OR "electroconvulsive therapy").ti,ab; 10477 results. 25. EMBASE; 23 OR 24; 17653 results. 26. EMBASE; 22 AND 25; 2381 results. 27. EMBASE; random*.ti,ab; 834585 results. 28. EMBASE; factorial*.ti,ab; 21436 results. 29. EMBASE; (crossover* OR cross-over*).ti,ab; 67175 results. 30. EMBASE; placebo*.ti,ab; 193225 results. 31. EMBASE; (doubl* ADJ blind*).ti,ab; 139175 results. 32. EMBASE; (singl* ADJ blind*).ti,ab; 13751 results. 33. EMBASE; assign*.ti,ab; 228671 results. 34. EMBASE; allocat*.ti,ab; 78482 results. 35. EMBASE; volunteer*.ti,ab; 171438 results. 36. EMBASE; CROSSOVER PROCEDURE/; 38027 results. 37. EMBASE; DOUBLE BLIND PROCEDURE/; 116871 results. 38. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 353239 results. 39. EMBASE; SINGLE BLIND PROCEDURE/; 18051 results. 40. EMBASE; 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39; 1352992 results. 41. EMBASE; 26 AND 40; 326 results.		
Medline	1. MEDLINE; "agitated adj3 depression".ti,ab; 0 results. 2. MEDLINE; DEPRESSIVE DISORDER, MAJOR/; 18932 results. 3. MEDLINE; "agitated depression".ti,ab; 113 results.	441	

	4. MEDLINE; ANXIETY/; 52051 results. 5. MEDLINE; agitat*.ti,ab; 12840 results. 6. MEDLINE; PSYCHOMOTOR AGITATION/; 3467 results. 7. MEDLINE; restless*.ti,ab; 5868 results. 8. MEDLINE; 4 OR 5 OR 6 OR 7; 71369 results. 9. MEDLINE; 2 OR 3 OR 8; 89649 results. 10. MEDLINE; ELECTROCONVULSIVE THERAPY/; 9441 results. 11. MEDLINE; (ECT OR "electroconvulsive therapy").ti,ab; 7945 results. 12. MEDLINE; 10 OR 11; 11882 results. 13. MEDLINE; 9 AND 12; 1121 results. 14. MEDLINE; "randomized controlled trial".pt; 380221 results. 15. MEDLINE; "controlled clinical trial".pt; 88687 results. 16. MEDLINE; randomized.ab; 293919 results. 17. MEDLINE; placebo.ab; 156349 results. 18. MEDLINE; "drug therapy".fs; 1728247 results. 19. MEDLINE; randomly.ab; 209713 results. 20. MEDLINE; trial.ab; 306538 results. 21. MEDLINE; groups.ab; 1334845 results. 22. MEDLINE; 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21; 3339978 results. 23. MEDLINE; 13 AND 22; 441 results.		
Summary	**NA**	**NA**	

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