Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In adults with psychotic depression, for how long should antipsychotics be prescribed following remission of symptoms, in improving rates of relapse, readmission rates and physical and social functioning?

Clarification of question using PICO structure

Patients: Adults with psychotic depression
Intervention: Continued treatment with antipsychotics
Comparator: Discontinuation of antipsychotics
Outcome: Remission, relapse, readmission and physical and social functioning

Clinical and research implications

One, short term, high quality RCT indicated that treatment with an antipsychotic in combination with an antidepressant may be more effective than treatment with an antidepressant alone, in achieving response and remission of depressive symptoms in hospitalised patients experiencing a major depressive episode with psychotic features.[1] A follow-up study, which continued the same medication in those patients who had responded during the initial RCT, indicated that response was maintained and remission rates increased over four months in all treatment groups; there were no significant differences between the groups during follow-up, i.e. only the difference already observed during the RCT phase was preserved.[2] There were two instances of relapse during the follow-up study, one in the imipramine group and one in the venlafaxine combined with quetiapine group.[2] We were unable to identify any study which compared continuation of antipsychotic treatment with discontinuation for remission, relapse, re-admission rates or physical and social functioning. No study provided information on the optimum prescribing duration for antipsychotics as an augmentation to antidepressants.

More RCTs are needed to establish the optimum prescribing duration for antipsychotics as an augmentation to antidepressants; the limited evidence currently available indicates only that treatment effects can be maintained by continuation of the same treatment regimen, it provides no information on whether antipsychotics could be withdrawn after an initial treatment period without loss of effect. Additional studies are also needed to establish the relative effectiveness of other combined antidepressant and antipsychotic treatment options. Trials should also be conducted in a

broader range of relevant populations; current evidence is limited to a hospitalised population experiencing an acute episode.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one RCT[1] with a four month, open-label follow-up study,[2] which reported data of partial relevance to this evidence summary. The RCT compared treatment with imipramine, venlafaxine alone, or venlafaxine in combination with quetiapine and reported response and remission rates as well as data on adverse events.[1] The follow-up study did not fully match the PICO criteria for this evidence summary, as patients continued on their study medications, i.e. there was no comparison of continuation versus discontinuation of antipsychotics.[2] The follow-up study provided data on response and remission rates over the longer term, as well as some minimal data on relapse rates.[2] No study was identified which reported rates of re-admission or assessed physical or social functioning.

Main Findings

One seven week RCT compared the effectiveness of imipramine, venlafaxine alone and venlafaxine in combination with quetiapine for the treatment of hospitalised adults who were experiencing a major depressive episode with psychotic features.[1] This trial found that venlafaxine combined with quetiapine was significantly more effective than venlafaxine alone in reducing depressive symptoms; the risk difference (RD) for a 50% or greater decrease from baseline in Hamilton Rating Scale for Depression (HAM-D) score was 32.5 (95%CI: 11.8 to 53.2) and the RD for a rating of 'much improved' or 'very much improved' on the Clinical Global Impression (CGI)-change scale was 30.3 (95%CI: 9.7 to 51.0).[1] There were no significant differences in response between the venlafaxine and imipramine groups, or between the venlafaxine combined with quetiapine and imipramine groups.[1] There was a borderline significant improvement in remission (HAM-D ≤7) rate associated with venlafaxine combined with quetiapine compared with imipramine; RD 20.0 (95%CI: 0.5 to 39.6).[1] There were no significant differences in remission rates between the venlafaxine and imipramine groups, or between the venlafaxine combined with quetiapine and venlafaxine only groups.[1] Incidence of 7% or greater weight gain was significantly higher in the venlafaxine combined with quetiapine than in the other two groups.[1] The follow-up study showed continuation of response and increased remission rates in all groups, with no significant differences between the groups, i.e. only the difference already observed during the RCT phase was preserved.[2] There were two instances of relapse during the follow-up study, one in the imipramine group and one in the venlafaxine combined with quetiapine group.[2]

Authors Conclusions

The RCT concluded that unipolar psychotic depression should be treated with a combination of an antidepressant and an antipsychotic rather than with an antidepressant alone, where the treatment combination in question is venlafaxine and quetiapine. However, the authors noted that it is uncertain whether their conclusions can be extended to other antidepressant and antipsychotic treatment combinations. The follow-up study, which continued the same medication in patients who had responded during the initial RCT, concluded that all treatments remained effective and well tolerated.

Reliability of conclusions/Strength of evidence

One, short term, high quality RCT indicated that treatment with an antipsychotic in combination with an antidepressant may be more effective than treatment with an antidepressant alone, for response and remission of depressive symptoms in hospitalised patients experiencing a major depressive episode with psychotic features.[1] A follow-up study, which continued the same medication in those patients who had responded during the initial RCT, indicated that response was maintained and remission rates increased over four months in all treatment groups; there were no significant differences between the groups during follow-up, i.e. only the difference already observed during the RCT phase was preserved.[2] There were two instances of relapse during the follow-up study, one in the imipramine group and one in the venlafaxine combined with quetiapine group.[2] We were unable to identify any study which compared continuation of antipsychotic treatment with discontinuation for remission, relapse, re-admission rates or physical and social functioning. No study provided information on the optimum prescribing duration for antipsychotics as an augmentation to antidepressants.

What do guidelines say?

NICE Clinical Guidelines CG90 states;

'For people who have depression with psychotic symptoms, consider augmenting the current treatment plan with antipsychotic medication (although the optimum dose and duration of treatment are unknown)' (NICE CG90 pg. 427).

The limited evidence identified for this summary does not add to or contradict that which informed current NICE guidance.

Date question received: 12/04/2013
Date searches conducted: 16/04/2013
Date answer completed: 06/05/2013

References

1. Wijkstra, J., Burger, H., Van, W. W. W., Birkenhager, T. K., Janzing, J. G., Boks, M. P., Bruijn, J. A., Van, M. L. M., Breteler, L. M., Verkes, R. J. & Nolen, W. A. 2010. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. Acta Psychiatrica Scandinavia, 121, 190–200.

2. Wijkstra, J., Burger, H., Van, W. W. W., Birkenhager, T. K., Janzing, J. G., Boks, M. P., Bruijn, J. A., Van, M. L. M., Breteler, L. M., Verkes, R. J. & Nolen, W. A. 2010. Long-term response to successful acute pharmacological treatment of psychotic depression. Journal of Affective Disorders, 123, 238-42.

Guidelines

3. The National Institute for Clinical Excellence. 2010. Depression. The treatment and management of depression in adults (updated edition). The British Psychological Society and The Royal College of Psychiatrists. http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf

Results

Primary Studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Wijkstra (2010a)	*Study design:* Multi-centre randomised controlled trial. *Population:* Hospitalised patients between the ages of 18-65, that met DSM-IV-TR criteria for a unipolar major depressive episode with psychotic features were eligible for inclusion in this study. Participants were required to score ≥18 on the Hamilton Rating Scale for Depression (HAM-D), at an initial screening visit and at baseline. Exclusion criteria were: acute indication for electroconvulsive therapy (ECT); mental retardation; alcohol or substance abuse or dependence within 3 months of enrolment; any serious somatic illness; somatic medication affecting mood; contraindications for study medication; adequate treatment of the current episode with imipramine (≥4 weeks with	n = 122 (imipramine n = 42, venlafaxine n = 39, venlafaxine + quetiapine n = 41)	This study aimed to determine whether patients with unipolar psychotic depression should be treated with the combination of an antidepressant and an antipsychotic or with an antidepressant alone. The mean age of study participants was approximately 50 years and approximately half were male. With the exception of gender (fewer female participants in the venlafaxine group) and duration of current episode (shorter in the imipramine group), there were no significant differences, in demographic characteristics or symptoms, between the three groups at baseline. 37% Of participants had previous exposure to an SSRI, 15% to a TCA and 8% to an inadequate dose of venlafaxine. All patients were without psychotropic medication for at least 4 days pre-study. The mean dose of imipramine, during the period of adequate dosing, was 254.4±101.1 mg/day, the mean maximum dose of venlafaxine in the venlafaxine only group was 372.3±14.2 mg/day, and in the venlafaxine + quetiapine group the mean maximum dose of venlafaxine was 373.4±11.2 mg/day and the mean maximum dose of quetiapine was 598.9±15.0 mg/day. Mean daily benzodiazepine use was similar across the three groups. For response on the HAM-D scale and response on the CGI scale, venlafaxine + quetiapine was significantly more effective than venlafaxine alone; RD 32.5 (95%CI: 11.8 to 53.2) and 30.3 (95%CI: 9.7 to 51.0), respectively. There were no significant differences in	Randomisation was conducted centrally, using a computer generated list and stratification for centre, using permuted blocks of six. The code was broken after the 7 week study (once all patient monitoring data were collected) and before the follow-up study, or during the 7 week study in case of medical emergency. The study used a double-blind, double-dummy design. Raters were also blind to treatment.

	adequate plasma levels) or venlafaxine (≥4 weeks ≥300 mg／day). *Intervention & comparison:* participants were randomised to 7 weeks treatment with either imipramine, venlafaxine, or venlafaxine & quetiapine. The study used a double dummy design, where all participants received both placebo and experimental intervention at alternating times. *Outcomes:* The primary outcome measure was response, defined as 50% decrease in HAM-D scores from baseline to study end-point, and a final HAM-D score of ≤14. Secondary outcomes were response on the Clinical Global Impression (CGI)-change scale (defined as 'much improved' or 'very much improved'), difference between treatment groups in mean change from baseline in HAM-D and CGI-severity scores, absence of psychotic features at end-point, and time to response. Although not a pre-defined		response rates between the imipramine and venlafaxine + quetiapine groups, or between the imipramine and venlafaxine only groups. Analysis of remission rates (HAM-D ≤7) indicated a borderline significant improvement associated with venlafaxine + quetiapine compared with imipramine; RD 20.0 (95%CI: 0.5 to 39.6). There were no significant differences in remission rates between the venlafaxine + quetiapine and venlafaxine only groups, or between the imipramine and venlafaxine only groups. Treatment by time interaction, in a linear mixed model, indicated that patients receiving the venlafaxine + quetiapine a 0.66 point per week faster mean decrease in HAM-D scores than those receiving venlafaxine. There were no significant differences in rate of decrease between the imipramine and venlafaxine + quetiapine groups, or between the imipramine and venlafaxine only groups. These patterns were similar for change in CGI. There were no significant differences between the treatment groups for any other secondary outcome measure. Twenty-two patients dropped out before completion of the study, six because of serious adverse events. Two drop-outs switched to hypomania (one in the imipramine and one in the venlafaxine + quetiapine group) and one switched to mania (imipramine group). Three further participants dropped out because of extra-pyramidal symptoms (imipramine), liver dysfunction (venlafaxine), and urine retention (venlafaxine + quetiapine). For non-serious adverse events, occurring in >10% of participants, dry mouth occurred more frequently in the imipramine than the venlafaxine group, and	All analyses were conducted on an intention-to-treat basis. Data were reported for all listed outcomes.

	outcome, remission rate, defined as HAM-D ≤7, was also analysed. Adverse events were also reported.		somnolence and tiredness both occurred more frequently in the venlafaxine + quetiapine group than in the venlafaxine only group. A weight gain of >7% occurred significantly more frequently in the venlafaxine + quetiapine group (35% of participants) than in the imipramine (3% of participants) or venlafaxine only (10% of participants) groups.	
Wijkstra (2010b)	This study was an open-label follow-up study to Wijkstra (2010a), described above. Participants in this study were those that completed the initial RCT as responders. Primary outcomes were maintainance of response (decrease in depressive symptoms on the HAM-D and CGI Scales). Secondary outcome measures were secondary outcome measures were remission rates (HAM-D≤7) and relapse rates (<50% decrease in HAM-D scores compared to baseline or a HAM-D score of >14). Psychotic symptoms, adverse events and weight gain were also recorded.	n = 59	This study aimed to asses to what extent response and remission rates as well as tolerability were maintained during follow-up and whether this differed between the treatment groups. During this 4 month follow-up study, all participants received open-label medication and it was advised to continue the same treatment as during the initial 7 week RCT. Participants were followed-up after 7 and 15 weeks (weeks 14 and 22). Most participants (94.7% at week 14 and 92.5% at week 22) continued their study medication. Most participants remained responders (94% of the imipramine group, 100% of the venlafaxine only group and 96% of the venlafaxine + quetiapine group); there were no significant differences between the groups. The overall remission rate increased during follow-up, from 59.3% at week 7 to 86.8% at week 22, with no significant differences between the groups. The HAM-D score decreased, from week 7 to week 22, in all groups, however, the decrease was not significant for the venlafaxine + quetiapine group.	This study was an open-label, follow-up study of the RCT described above.

			Occurrence of adverse events was slightly lower than during the 7 week RCT, with no significant differences between the groups. Weight gain increased in all groups during follow-up. Only two participants relapsed during follow-up, one I the imipramine group and one in the venlafaxine + quetiapine group.	

Risk of Bias: SRs

Primary studies

Study	RISK OF BIAS					
	Random allocation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective Reporting**
Wijkstra (2010a)	☺	☺	☺	☺	☺	☺
Wijkstra (2010b)	Not applicable; this is study was an open label, follow-up study of the RCT described above.					

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Psychotic depression	59	
DARE	((psychosis OR psychotic OR schizo*) adj5 depress*) in DARE	66	
Primary studies			
CENTRAL	MeSH descriptor: [Affective Disorders, Psychotic] explode all trees 1468 #2 Enter terms for search psychosis or psychoticpsychosis or psychotic 4570 #3 Enter terms for search hallucinations or hallucinatinghallucinations or hallucinating 972 #4 Enter terms for search delusions or delusionaldelusions or delusional 574 #5 Enter terms for search #1 or #2 or #3 or #4#1 or #2 or #3 or #4 6464 #6 MeSH descriptor: [Depressive Disorder, Major] explode all trees 2006 #7 Enter terms for search depressdepress 6834 #8 Enter terms for search #6 or #7#6 or #7 8238 #9 Enter terms for search #5 and #8#5 and #8 735 #10 MeSH descriptor: [Treatment Outcome] explode all trees 80589 #11 Enter terms for search relapse 14277 #12Enter terms for searcremission10701 #13Enter terms for searcreadmission2077 #14Enter terms for searc#10 or #11 or #12 or #1399126 #15Enter terms for searc#9 and #14 360 Central only 171	171	
PsycINFO	1. PsycINFO; exp PSYCHOSIS/; 86457 results. 2. PsycINFO; psychotic.ti,ab; 29691 results. 3. PsycINFO; hallucinat*.ti,ab; 10877 results.	29	

	4. PsycINFO; delusion*.ti,ab; 10794 results. 5. PsycINFO; 1 OR 2 OR 3 OR 4; 109540 results. 6. PsycINFO; MAJOR DEPRESSION/; 79727 results. 7. PsycINFO; depress*.ti,ab; 197108 results. 8. PsycINFO; 6 OR 7; 200130 results. 9. PsycINFO; 5 AND 8; 15393 results. 10. PsycINFO; "psychotic depression".ti,ab; 907 results. 11. PsycINFO; (psychotic adj2 depression).ti,ab; 1385 results. 12. PsycINFO; 10 OR 11; 1385 results. 13. PsycINFO; 9 OR 12; 15393 results. 14. PsycINFO; exp NEUROLEPTIC DRUGS/; 23690 results. 15. PsycINFO; antipsychotic*.ti,ab; 18977 results. 16. PsycINFO; 14 OR 15; 30086 results. 17. PsycINFO; 13 AND 16; 1794 results. 18. PsycINFO; MAINTENANCE THERAPY/ OR RELAPSE PREVENTION/ OR TREATMENT DURATION [+NT]/; 5574 results. 19. PsycINFO; SYMPTOM REMISSION/; 342 results. 20. PsycINFO; relapse.ti,ab; 14506 results. 21. PsycINFO; readmission.ti,ab; 1206 results. 22. PsycINFO; "length of treatment".ti,ab,ti; 634 results. 23. PsycINFO; 18 OR 19 OR 20 OR 21 OR 22; 20137 results. 24. PsycINFO; 17 AND 23; 97 results. 25. PsycINFO; CLINICAL TRIALS/; 6674 results. 26. PsycINFO; random*.ti,ab; 117636 results. 27. PsycINFO; groups.ti,ab; 342064 results. 28. PsycINFO; (double adj3 blind).ti,ab; 16783 results. 29. PsycINFO; (single adj3 blind).ti,ab; 1267 results. 30. PsycINFO; EXPERIMENTAL DESIGN/; 8599 results. 31. PsycINFO; controlled.ti,ab; 73371 results. 32. PsycINFO; (clinical adj3 study).ti,ab; 7249 results. 33. PsycINFO; trial.ti,ab; 61920 results. 34. PsycINFO; "treatment outcome clinical trial".md; 23767 results. 35. PsycINFO; 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34; 526881 results.		

	36. PsycINFO; 24 AND 35; 29 results.		
Embase	25. EMBASE; exp PSYCHOSIS/; 195412 results. 26. EMBASE; psychotic.ti,ab; 30035 results. 27. EMBASE; hallucinat*.ti,ab; 12656 results. 28. EMBASE; delusion*.ti,ab; 10278 results. 29. EMBASE; 25 OR 26 OR 27 OR 28; 203640 results. 30. EMBASE; MAJOR DEPRESSION/; 31425 results. 31. EMBASE; depress*.ti,ab; 356378 results. 32. EMBASE; 30 OR 31; 362743 results. 33. EMBASE; 29 AND 32; 25872 results. 34. EMBASE; "psychotic depression".ti,ab; 934 results. 35. EMBASE; (psychotic adj2 depression).ti,ab; 1489 results. 36. EMBASE; 34 OR 35; 1489 results. 37. EMBASE; 33 OR 36; 25872 results. 38. EMBASE; exp NEUROLEPTIC DRUGS/; 0 results. 39. EMBASE; antipsychotic*.ti,ab; 34852 results. 40. EMBASE; 38 OR 39; 34852 results. 41. EMBASE; 37 AND 40; 2676 results. 42. EMBASE; MAINTENANCE THERAPY/ OR RELAPSE PREVENTION/ OR TREATMENT DURATION [+NT]/; 104116 results. 43. EMBASE; SYMPTOM REMISSION/; 0 results. 44. EMBASE; relapse.ti,ab; 101275 results. 45. EMBASE; readmission.ti,ab; 9531 results. 46. EMBASE; "length of treatment".ti,ab,ti; 1927 results. 47. EMBASE; 42 OR 43 OR 44 OR 45 OR 46; 211444 results. 48. EMBASE; 41 AND 47; 302 results. 49. EMBASE; random*.ti,ab; 795046 results. 50. EMBASE; factorial*.ti,ab; 20523 results. 51. EMBASE; (crossover* OR cross-over*).ti,ab; 65083 results. 52. EMBASE; placebo*.ti,ab; 187093 results. 53. EMBASE; (doubl* ADJ blind*).ti,ab; 135490 results. 54. EMBASE; (singl* ADJ blind*).ti,ab; 13172 results. 55. EMBASE; assign*.ti,ab; 219160 results. 56. EMBASE; allocat*.ti,ab; 74396 results. 57. EMBASE; volunteer*.ti,ab; 166113 results.	84	

	58. EMBASE; CROSSOVER PROCEDURE/; 36637 results. 59. EMBASE; DOUBLE BLIND PROCEDURE/; 114019 results. 60. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 340260 results. 61. EMBASE; SINGLE BLIND PROCEDURE/; 17227 results. 62. EMBASE; 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61; 1296745 results. 63. EMBASE; 48 AND 62; 109 results. 64. EMBASE; exp ATYPICAL ANTIPSYCHOTIC AGENT/; 66860 results. 65. EMBASE; 39 OR 64; 80729 results. 66. EMBASE; 37 AND 65; 4934 results. 67. EMBASE; 62 AND 66; 1021 results. 68. EMBASE; 67 [Limit to: Exclude MEDLINE Journals]; 84 results.		
Medline	25. MEDLINE; exp PSYCHOSIS/; 36460 results. 26. MEDLINE; psychotic.ti,ab; 21604 results. 27. MEDLINE; hallucinat*.ti,ab; 9285 results. 28. MEDLINE; delusion*.ti,ab; 7541 results. 29. MEDLINE; 25 OR 26 OR 27 OR 28; 60039 results. 30. MEDLINE; MAJOR DEPRESSION/; 0 results. 31. MEDLINE; depress*.ti,ab; 293150 results. 32. MEDLINE; 30 OR 31; 293150 results. 33. MEDLINE; 29 AND 32; 8605 results. 34. MEDLINE; "psychotic depression".ti,ab; 739 results. 35. MEDLINE; (psychotic adj2 depression).ti,ab; 1124 results. 36. MEDLINE; 34 OR 35; 1124 results. 37. MEDLINE; 33 OR 36; 8605 results. 38. MEDLINE; exp NEUROLEPTIC DRUGS/; 116807 results. 39. MEDLINE; antipsychotic*.ti,ab; 24178 results. 40. MEDLINE; 38 OR 39; 123592 results. 41. MEDLINE; 37 AND 40; 1562 results. 42. MEDLINE; MAINTENANCE THERAPY/ OR RELAPSE PREVENTION/ OR TREATMENT DURATION [+NT]/; 0 results.	95	

	43. MEDLINE; SYMPTOM REMISSION/; 0 results. 44. MEDLINE; relapse.ti,ab; 74016 results. 45. MEDLINE; readmission.ti,ab; 6604 results. 46. MEDLINE; "length of treatment".ti,ab,ti; 1449 results. 47. MEDLINE; 42 OR 43 OR 44 OR 45 OR 46; 81863 results. 48. MEDLINE; 41 AND 47; 95 results. 49. MEDLINE; "maintenance therapy".ti,ab; 8292 results. 50. MEDLINE; "treatment duration".ti,ab; 4869 results. 51. MEDLINE; 44 OR 45 OR 46 OR 49 OR 50; 93227 results. 52. MEDLINE; 41 AND 51; 110 results. 53. MEDLINE; "randomized controlled trial".pt; 347102 results. 54. MEDLINE; "controlled clinical trial".pt; 85770 results. 55. MEDLINE; randomized.ab; 264978 results. 56. MEDLINE; placebo.ab; 143370 results. 57. MEDLINE; "drug therapy".fs; 1601703 results. 58. MEDLINE; randomly.ab; 192903 results. 59. MEDLINE; trial.ab; 273597 results. 60. MEDLINE; groups.ab; 1244625 results. 61. MEDLINE; 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60; 3102686 results. 62. MEDLINE; 52 AND 61; 95 results.		
Summary	**NA**	**NA**	

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