Chapter 2

Pharmacological treatment for unipolar psychotic depression
Systematic review and meta-analysis

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Abstract

Objective: The optimal pharmacological treatment of unipolar psychotic depression is uncertain.

Method: Systematic review and meta-analysis of randomised controlled trials (RCT).

Results: Ten trials were included in the review. We found no evidence that the combination of an antidepressant with an antipsychotic is more effective than an antidepressant alone. This combination was statistically more effective than an antipsychotic alone.

Conclusion: Antidepressant monotherapy, and adding an antipsychotic if the patient does not respond or starting with the combination of an antidepressant and an antipsychotic both appear to be appropriate options for patients with unipolar psychotic depression. However, clinically the balance between risks and harms may suggest the first option should be preferred for many patients. Starting with an antipsychotic alone appears to be inadequate.
Introduction

For unipolar psychotic depression, in which psychotic features appear in the context of a major depressive episode, electroconvulsive therapy (ECT) is considered by many clinicians to be the most effective and therefore the first line treatment. Pharmacotherapy is also often considered a suitable first line treatment, because many patients prefer drug therapy to ECT, and moreover, after a successful course of ECT subsequent treatment with medication is often needed to prevent relapse. If the choice is pharmacotherapy, it is unclear whether one can start with an antidepressant alone or should combine it with an antipsychotic. Some reviews suggest that one may consider antidepressant monotherapy before adding an antipsychotic.1,2 However, recent US and British guidelines recommend the combination.3,4

We report a systematic review of the evidence regarding the pharmacological treatment of unipolar psychotic depression.

Method

This review was performed as a Cochrane systematic review in co-operation with the Cochrane Collaboration Depression, Anxiety and Neurosis group, London, United Kingdom.5

Included studies

We included randomised controlled trials (RCTs) of the pharmacological treatment of patients with psychotic depression, published in any language. We expected to identify very few RCTs with the treatment of psychotic depression as primary focus. We therefore also selected RCTs including patients with major depression with and without psychotic features, in which the effects in the subgroup of patients with psychotic depression were reported separately. The inclusion criteria for the review were:

Participants

We included RCTs investigating patients in any setting (in-patients and out-patients) with a unipolar major depressive disorder having a current major depressive episode with psychotic features. If a trial had studied patients with depressive episodes in the course of a bipolar disorder, it was only included if the results in non-bipolar depression group were reported separately or if the percentage of patients with bipolar depression did not exceed 20% of the total study population.
**Interventions**

We included RCTs making the following comparisons: antidepressant \( v. \) antidep-
pressant, antipsychotic \( v. \) antipsychotic, antidepressant \( v. \) placebo, antipsychotic \( v. \) placebo, antidepressant \( v. \) antipsychotic, antidepressant plus antipsychotic \( v. \) anti-
depressant, antidepressant plus antipsychotic \( v. \) antipsychotic, antidepressant plus antipsychotic \( v. \) placebo.

**Search strategy for identification of studies**

Bibliographic databases such as MEDLINE do not have an indexing term for psy-
chotic depression. We therefore screened all RCTs that had included patients with
a unipolar major depressive disorder to identify those possibly including patients
with psychotic features.

We searched the Cochrane Central Register of Controlled Trials (CENTRAl) with the terms depressive disorder and drug-treatment. In addition we
searched MEDLINE (1966 until April 2004) and EMBASE (1980 until April
2004) using the following terms: (“depressive disorder/drug therapy”[MESH]
AND (“delusions”[MESH Terms] OR delusions[Text Word]) OR (“psychotic
disorders”[MESH Terms] OR psychotic[Text Word]) AND features[All Fields])))
combined with a search strategy for RCTs.

In step 1 of the search process, all abstracts of the identified publications
were screened independently by two authors (50% by both JW and JL, 50% by both
FB and WN) and studies were selected if they met the following criteria:
(a) the study was a randomised controlled trial;
(b) included patients with a major depressive disorder;
(c) investigated the effectiveness of pharmacological treatment; and
(d) concerned acute phase treatment.

In case of any doubt or disagreement between the reviewers, the pu-
блиcation was included. Next, the full articles were obtained for the selected ab-
stracts. In step 2, a trained medical student screened these full articles to select
all trials in which: (a) patients with psychotic depression were not excluded; and
(b) results in the subgroup of patients with psychotic depression were reported
separately.

In case of any doubt the publication was included. In order to check the
reliability of this procedure a random number of 60 articles were also screened
by JW, which revealed no publications that had not been selected by the medical
student. In addition, reference lists of included publications, related reviews and
abstract books of recent congresses were searched and trials were identified via
personal communication. In step 3, two authors (JW, FB) independently reviewed
all identified publications according to the inclusion criteria. Any disagreement was resolved by consensus discussion with another co-author (WN).

Quality assessment

Two reviewers (JW and JL) assessed the methodological quality of the included trials, according to the criteria of the Cochrane Collaboration. These criteria focus on randomisation procedure (especially allocation concealment and randomisation); whether the study was double-blind, single-blind or open randomised; analysis (stratification prior to treatment or non-stratification of psychotic v. non-psychotic patients in the RCTs which had not the treatment of psychotic depression as main focus); and other aspects such as reporting of the number of patients leaving the trial and the reasons for the withdrawals.

Types of outcome measures

The primary efficacy outcome used in the analysis was clinical response based on observer rated symptom reduction, for example a reduction of at least 50% on the Hamilton Rating Scale for Depression (HRSD) or any other observer-rated depression severity rating scale, or a change score on the Clinical Global Impression-Change (CGI-C) of ‘much improved’ or ‘very much improved’). As secondary efficacy outcomes, we investigated: remission as defined in the reports and based on the HRSD or other observer-rated depression severity scale or change from baseline in score on the HRSD or observer depression severity rating scale or change in severity on Clinical Global Impression-Severity (CGI-S); and quality of life.

The primary harm outcome used in the analysis was overall withdrawal rate during acute treatment as a proxy measure of overall acceptability of treatment. We also analysed withdrawal rates resulting from adverse effects, all cause mortality and suicide.

Data extraction

Data were extracted on participant’s characteristic, diagnosis (diagnostic instrument, classification), intervention details, and outcome measures. Data were extracted independently by two reviewers (JW and JL).

Data analysis

Data were entered into RevMan 4.2. For binary efficacy outcomes a relative risk (with 95% confidence intervals) was calculated for each comparison. When neces-
sary, we converted response data from the trials into intention-to-treat response data by using the total number of randomised patients per group who had started with treatment as the denominator.

Results

Description of the studies

From the search in the Cochrane Central Register of Controlled Trials (CENTRAL) we identified 1782 publications. The searches in MEDLINE and EMBASE resulted in 720 and 831 publications, respectively. The first step of screening the abstracts of these publications resulted in 789 publications (749 from CENTRAL, 38 from MEDLINE, and 11 from EMBASE). The second step of screening the full articles resulted in the identification of 52 publications (47, 3 and 2 respectively). Hand-searching of reference lists of relevant reviews resulted in one further publication, whereas hand-searching of the included publications revealed in no other publication. The third step of reviewing these 53 publications resulted in seven included studies. Finally, we added two other publications from which we knew were then in press: one by Van den Broek et al and one by Rothschild et al reporting two similar trials. Thus, nine publications with a total of ten RCTs were included. (See table 1)
Table 1 Characteristics of randomised, controlled trials of pharmacological treatment for psychotic depression

<table>
<thead>
<tr>
<th>Study and year</th>
<th>N</th>
<th>Randomisation/ Blinding</th>
<th>Drug comparison</th>
<th>Dose (blood level)</th>
<th>Additional medication</th>
<th>Treatment period</th>
<th>Diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton et al, 1990</td>
<td>46</td>
<td>Not described/ Described</td>
<td>Amoxapine vs amitriptyline + perphenazine</td>
<td>300-500 mg versus 150-250 mg + 24.40 mg. No blood levels.</td>
<td>Lorazepam, oxazepam in ‘low dose’</td>
<td>4 weeks</td>
<td>DSM-III: psychotic depressive episode</td>
<td>&gt; 50% reduction in Hamilton Rating Scale of Depression-17</td>
</tr>
<tr>
<td>Bruijn et al, 1996</td>
<td>30</td>
<td>Not described/ Described</td>
<td>Imipramine versus mirtazapine</td>
<td>37.5-450 mg (199-400 ng/ml) vs 40-100 mg (49-93 ng/ml)</td>
<td>Valerian, lorazepam 1-5 mg, haloperidol 1-15 mg a day</td>
<td>4 weeks after reaching predefined blood levels</td>
<td>DSM-III-R: depressive episode Subgroup: psychotic</td>
<td>≥ 50% reduction in HRSD-17</td>
</tr>
<tr>
<td>Mulsant et al, 2001</td>
<td>36</td>
<td>Not described/ Described</td>
<td>Nortriptyline vs nortriptyline + perphenazine</td>
<td>Mean: 76 mg (101 ng/ml) vs 63 mg (120 ng/ml) + 19 mg (4 ng/ml)</td>
<td>Lorazepam as needed</td>
<td>After randomisation 2-16 weeks (at least 4 weeks)</td>
<td>DSM-III-R: psychotic major depressive disorder</td>
<td>HRSD-17 &lt; 11 + Brief Psychiatric Rating Scale (11,12,15) 1 or 2</td>
</tr>
<tr>
<td>Rothschild et al, 2004 a</td>
<td>124</td>
<td>Not described/ Not described</td>
<td>Olanzapine vs olanzapine + fluoxetine</td>
<td>Mean: 11.9 mg vs 12.4 mg + 23.5 mg vs placebo No blood levels</td>
<td>Mean 30 mg a day diazepam</td>
<td>8 weeks</td>
<td>DSM-IV: major depression with psychotic features</td>
<td>≥ 50% reduction in HRSD-24</td>
</tr>
<tr>
<td>Rothschild et al, 2004 b</td>
<td>125</td>
<td>Not described/ Not described</td>
<td>Idem</td>
<td>Mean: 14.0 mg vs 13.9 mg + 22.6 mg</td>
<td>Idem</td>
<td>Idem</td>
<td>Idem</td>
<td>Idem</td>
</tr>
<tr>
<td>Spiker et al, 1985</td>
<td>58</td>
<td>Partly described/ Described</td>
<td>Perphenazine vs amitriptyline vs amitriptyline + perphenazine</td>
<td>Mean 50 mg (19-113 ng/ml) vs 218 mg (ami + nor 130-500 ng/ml) vs 170 mg (157-690 ng/ml) + 54 mg (18-128 ng/ml)</td>
<td>Benztropine mesylate 4 mg</td>
<td>4 weeks</td>
<td>SADS and RDC major depressive disorder (only with delusions).</td>
<td>HRSD-17 &lt; 7 + Delusional Rating Score = 1 (6 point scale in the Schizophrenia and Affective Disorder Scale)</td>
</tr>
</tbody>
</table>

*Note: HRSD-24 refers to Hamilton Rating Scale for Depression-24.*
<table>
<thead>
<tr>
<th>Study and year</th>
<th>N</th>
<th>Randomisation/ Blinding</th>
<th>Drug comparison</th>
<th>Dose (blood level)</th>
<th>Additional medication</th>
<th>Treatment period</th>
<th>Diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiker et al, 1988³⁹</td>
<td>27</td>
<td>Not described/ Described</td>
<td>Amitriptyline versus placebo</td>
<td>3 days 50; 4 days 100; 7 days 150, 14 days 200 mg. No blood levels</td>
<td>None</td>
<td>4 weeks (at least 3 weeks ≥ 150 mg)</td>
<td>DSM III: major depressive disorder</td>
<td>HRSD-17 &lt; 7 + not psychotic or 6.5 - 9.5 + not psychotic + ≤ 1/3 entering score</td>
</tr>
<tr>
<td>Van den Broek et al, 2004⁷</td>
<td>48</td>
<td>Described/ Described</td>
<td>Imipramine vs fluvoxamine</td>
<td>150-450 mg (imi + desimi 192-521 ng/ml). Vs 150-1800 mg (109-325 ng/ml).</td>
<td>Valerian, lorazepam 1-3 mg, haloperidol 1-10 mg a day</td>
<td>4 weeks after reaching pre-defined blood levels</td>
<td>DSM-IV: major depressive disorder</td>
<td></td>
</tr>
<tr>
<td>Subgroup: psychotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 50% reduction in HRSD-17</td>
</tr>
<tr>
<td>Zanardi et al, 1996⁴</td>
<td>32</td>
<td>Not described/ Not described</td>
<td>Sertraline versus paroxetine</td>
<td>150 mg vs 50 mg from day 8. No blood levels</td>
<td>Flurazepam &lt;30 mg</td>
<td>5 weeks</td>
<td>DSM-III-R: psychotic depressive episode</td>
<td>HRSD-21 &lt; 8 + not psychotic</td>
</tr>
<tr>
<td>Zanardi et al, 2000⁴</td>
<td>22</td>
<td>Not described/ Not described</td>
<td>Venlafaxine versus fluvoxamine</td>
<td>300 mg versus 300 mg. No blood levels</td>
<td>Flurazepam &lt;30 mg</td>
<td>5 weeks</td>
<td>DSM-III-R: psychotic depressive episode</td>
<td>HRSD-21 &lt; 9 + not psychotic</td>
</tr>
</tbody>
</table>

BPRS, Brief Rating Scale; HRSD, Hamilton Rating Scale for Depression; RDC, Research Diagnostic Criteria; SADS, Schedule for Affective Disorders and Schizophrenia
In seven of the ten studies the treatment of psychotic depression was the primary focus. From three studies we used data from the subgroup of patients with psychosis, which were reported separately.7,9,10

Five RCT did not include only patients with unipolar psychotic depression. In the study by Zanardi et al11 it was possible to exclude the data relating to participants with bipolar disorder. The study by Anton & Burch12 reported 15.8% (6 out of 38) cases of bipolar disorder, and it is unclear how many of the 8 participants who left the study and whose data were excluded before analysis had bipolar disorder. To solve this problem we assumed a random withdrawal rate. In Spiker et al13 15.5% of the patients in the results had bipolar disorder. In Bruijn et al10 and Zanardi et al14 we were able to exclude the data for patients with bipolar disorder with the help of additional information from the authors.

Outcome measures

It was not possible to transfer the authors’ defined response data into rates based on one definition (e.g. 50% reduction of the HRSD score). In addition, several authors used response definitions based on what is often considered remission. In the absence of a better option, we decided to use only response data as reported by the authors.

In eight of the ten studies we recalculated intention-to-treat response rates using all randomised patients as the denominator. We thus included many patients who were excluded from analyses by the original researchers: from the study of Anton & Buch14 8 patients who left the study before receiving a 2 full weeks of active medication; 9 and 3 patients, respectively from the studies of Bruijn et al10 and Van den Broek et al7 who were treated with haloperidol; from the study of Mulsant et al15 6 patients who left the trial after randomisation; 7% and 9% of the randomised patients respectively from the two trials of Rothschild et al,8 who left the trial between baseline and the first visit after start of treatment at week 1; and finally 7 patients who left the studies of Spiker et al13 and Spiker & Kupfer.9 Extracting continuous data of observer-rated depression severity scales for analysis was impossible because we were not able to convert these data according to an intention-to-treat analysis7,8,9,10,12,13,15 and in the two other studies11,14 no continuous data were given. Other efficacy outcome measures (e.g. change in quality of life) could not be extracted from the trials.

Overall rates of withdrawal were available for all studies. Rates of withdrawal because of adverse effects were available in four studies7,12,13,15 in three other studies these data were not based on an intention-to-treat analysis8,8,9 were not available in one study (SK 1988) and were the same as the overall withdrawal rates in two studies11,14. Withdrawals specifically owing to death or suicide were not reported in any of the studies.
Efficacy analyses

Only one RCT compared an antidepressant with a placebo. In this study amitriptyline was not statistically significantly more effective than placebo (RR 8.40, 95% CI 0.50 - 142.27, P=0.14).

In four studies, two different antidepressants were compared directly. In one study, imipramine under plasma level control was statistically significantly more effective than mirtazapine (RR 3.00, 95% CI 1.01 - 8.95, P=0.05). In another, imipramine under plasma level control was statistically significantly more effective than fluvoxamine (RR 2.10, 95% CI 1.06-4.17, P=0.03). In the first study by Zanardi et al, sertraline was statistically significantly more effective than paroxetine (RR 3.37, 95% CI 1.19 - 9.57, P=0.02); the second study by Zanardi et al did not find a statistically significant difference between fluvoxamine and venlafaxine.

In two studies the tricyclic antidepressant (TCA) imipramine given under plasma level control was compared to an antidepressant of another class (mirtazapine or fluvoxamine). After pooling these studies, imipramine was statistically significant superior to the non-TCA (RR 2.36, 95% CI 1.32 - 4.23, P=0.004) (Fig. 1).

In three RCTs selective serotonin reuptake inhibitors (SSRI) were studied. Response rates to these SSRIs varied from 21.4% (paroxetine) and 30.4% (fluvoxamine) to 72.2% (sertraline) and 81.8% (fluvoxamine). In one of these studies there was a statistically significant difference between two SSRIs, favouring sertraline. Combining the studies with SSRIs led to a mean response rate to SSRIs of 51.5%. A pooled comparison of SSRIs with other antidepressants was not possible.

One study comparing antidepressant monotherapy (amitriptyline) with antipsychotic monotherapy (perphenazine) did not find a statistically significant difference (RR 2.09, 95% CI 0.64 - 6.82, P=0.22).

We found two studies comparing antipsychotic monotherapy (olanzapine) with placebo. Pooling these studies did not show a statistically significant difference (RR 1.13, 95% CI 0.74 - 1.73, P=0.57).

In two studies the combination of an antidepressant (nortriptyline or amitriptyline) and an antipsychotic (perphenazine) was compared with antidepressant monotherapy. Pooling these two studies did not show a statistically significant difference between a TCA plus an antipsychotic and a TCA alone (RR 1.44, 95% CI 0.86 - 2.41, P=0.16) (Fig. 2).
**Figure 1** Efficacy of a tricyclic antidepressant (TCA) monotherapy v. non-tricyclic antidepressant (non-TCA) monotherapy

**Figure 2** Efficacy of the combination of a tricyclic antidepressant (TCA) + a classical antipsychotic (CAP) versus TCA monotherapy
In three studies the combination of an antidepressant and an antipsychotic was compared with antipsychotic monotherapy. In one of these studies\textsuperscript{13} the combination of amitriptyline plus perphenazine was statistically significantly superior to perphenazine alone (RR 3.61, 95\% CI 1.23 - 10.56, \(P=0.02\)). In the other two studies comparing the combination of olanzapine plus fluoxetine\textsuperscript{8} with olanzapine alone, pooling resulted in a significant advantage for the combination over the antipsychotic alone (RR 1.64, 95\% CI 1.10 - 2.44, \(P=0.01\)) and over placebo (RR 1.86, 95\% CI 1.23 - 2.82, \(P=0.003\)). Pooling the data from all three studies comparing the combination of an antidepressant plus an antipsychotic with an antipsychotic alone showed a statistically significant difference favouring the combination (RR 1.92, 95\% CI 1.32 - 2.80, \(P=0.0007\)) (Figure 3).
**Figure 3** Efficacy of the combination of an antipsychotic (AP) + an antidepressant (AD) versus antipsychotic monotherapy
Other analyses

The rates of withdrawal from the studies varied from 9% to 41%. In the two multicentre trials with olanzapine/fluoxetine the rate was 102 out of 249 (41%), and these authors reported even higher non-completion rates (completers: 110 out of 249 = 44%, thus the non-completion rate was 56%). There was no statistically significant difference in the overall dropout rates between any of the treatments, either in individual studies or after pooling of studies.

Discussion

Despite our extensive search of the literature, we identified very few RCTs investigating the pharmacological treatment of patients with a unipolar major depressive episode with psychotic features (psychotic depression). In addition to seven trials in which the treatment of patients with a psychotic depression was the major focus of the study, we were able to find three other trials that reported on the effects in a subgroup of patients with psychotic depression separately. The authors of two of these studies of both psychotic and non-psychotic depression provided us with additional information on the results in the subgroups of patients with psychotic depression. Because of the numbers involved, we were not able to approach the authors of all RCTs comprising depressed patients to request similar information. However, if data from other RCTs on the subgroup of people with psychotic depressions are available, we invite the authors of these trials to provide us with the relevant data, so that we may update this systematic review.

Underinvestigation of unipolar psychotic depression

That we identified only ten RCTs in psychotic depression illustrates that this most severe form of depression is seriously underinvestigated. One probable reason for this is that it is difficult to conduct RCTs in patients with a psychotic depression. These patients not only have a psychotic illness, but often also very anxious or physically ill. In addition, they are often offered ECT directly because many clinicians assume that ECT is more effective than pharmacotherapy. Patients with psychotic depressive illness may also be unable to give informed consent or may tend to withdraw from trials. Furthermore - until the recent trials by Rothschild et al - pharmaceutical companies were not interested in conducting trials in psychotic depression because this subgroup of depression is not considered a separate indication for treatment by the regulatory authorities and therefore commercially unattractive.
Implications of the study

Despite the paucity of RCTs, a few clinically relevant conclusions can be drawn: First, there is no evidence for the clinical belief that an antidepressant alone is ineffective in psychotic depression. In seven of the ten studies there was at least one treatment arm with an antidepressant as monotherapy, with in total 11 treatment arms. In 5 of these treatment arms the antidepressant was effective in more than 50% of the patients: imipramine, imipramine, sertraline, fluvoxamine as well as venlafaxine. In three studies there was even a statistically significant difference between two antidepressants. In two of these studies imipramine (under plasma level control) was more effective than fluvoxamine and mirtazapine respectively, suggesting that a tricyclic antidepressant is to be preferred over non-tricyclic drug in patients with a psychotic depression. This finding is in line with the three Danish studies among hospitalised depressed patients in which clomipramine was more effective than citalopram, paroxetine or moclobemide respectively. In these three studies, patients with psychotic depression were also included; unfortunately, however, it is not possible to identify which patients these were, as this information was not systematically recorded. In the third trial finding a difference between two antidepressants, more patients responded to sertraline than to paroxetine, probably related to more patients withdrawing from the paroxetine group. It is difficult to draw a conclusion from this study, as in another study the same group found good response rates to another SSRI, fluvoxamine as well as to venlafaxine.

Second, there is no evidence that the combination of an antidepressant with an antipsychotic is more effective than an antidepressant alone. Therefore, it can be concluded that the recommendation in the US and British guidelines that in psychotic depression the combination should be preferred over an antidepressant alone is not reliably evidence based, if not necessarily incorrect. Clinically, the balance between risks and harms may suggest that initial monotherapy with an antidepressant should be the preferred option for many patients.

Finally, there is evidence that the combination of an antidepressant with an antipsychotic is more effective than an antipsychotic alone. This was the major result of the study comparing amitriptyline plus perphenazine v. perphenazine alone and was also found in one of the studies comparing fluoxetine plus olanzapine v. olanzapine alone. Moreover, it was confirmed in the pooled analysis of these studies. Therefore, it is concluded that one should not start with antipsychotic monotherapy.

Limitations

Our review has several limitations. First, none of the studies with antidepressant monotherapy had a sample size exceeded 25 patients per group. The only two rela-
tive large studies were the studies sponsored by Eli Lilly\textsuperscript{8} with around 50 patients per group (olanzapine 48 and 53 patients, and placebo 51 and 49 patients respectively), but with fewer patients in the group receiving olanzapine plus fluoxetine (25 and 23 respectively). As with all systematic reviews, publication bias is a potentially serious source of error. There were too few studies - especially too few larger studies - to investigate further the possibility of publication bias and so it cannot be ruled out. Additionally, the relative high proportion of these small studies (5 out of 10) reporting a significant difference between two treatments, suggests publication bias.

Second, we could only use one outcome measure regarding efficacy: the response rates as defined by the authors. It was impossible to recalculate these response rates into a standard response rate based on one definition (e.g. HRSD-17 scores), as many studies used other versions of the HRSD or actually reported only remission rates. As some of these authors’ response definitions may actually be considered remission, this might have had an influence on the results of our meta-analysis.

Finally, there was considerable clinical heterogeneity between the trials, illustrated by substantial differences in response rates to antidepressant monotherapy between the European and the US studies. Two Italian studies\textsuperscript{11,14} reported high response rates (above 50\%) to SSRIs (with the exception of paroxetine), and in both the Dutch studies\textsuperscript{7,10} the response rate was above 50\% to imipramine (but not to mirtazapine and fluvoxamine). In contrast, the US studies reported response rates below 50\%.\textsuperscript{9,13,15} One likely reason for this US-European discrepancy is differences between the study populations. Although all studies required that patients fulfilled diagnostic criteria according to a specified diagnostic classification, the reliability of diagnosis may have been limited in some - if not most - of the trials. Only four trials used a semi-structured interview,\textsuperscript{7,10,13,15} and only one of these trials\textsuperscript{10} reported the specific psychotic features for all patients. This leaves open the possibility that the conclusion that in a particular patient (for instance) a feeling of guilt was actually a delusion was drawn differently across the trials in this review. A similar problem may have played a part in the judgement as to whether a patient had a psychotic depression in the course of unipolar disorder or bipolar disorder.

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