Pharmacological treatment of psychotic depression
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Chapter 7

Treatment of unipolar psychotic depression
An open study of lithium addition in refractory psychotic depression

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Abstract

Objective: This study was designed to compare the efficacy of three two-phase pharmacological treatment strategies for inpatients with DSM-IV-TR major depressive disorder with psychotic features.

Method: During phase I, 122 patients participated in a 7 week double-blind eight center study comparing imipramine (dose adjusted to target plasma levels of 200-300 ng/ml), venlafaxine (maximum 375 mg/day) and venlafaxine-quetiapine (maximum 375 mg/day; 600 mg/day). Four centers participated in phase II. In phase II, for patients without treatment response or with partial response, lithium was added to phase I pharmacotherapy. Lithium dose was adjusted to a target serum level of 0.6-1.0 mmol/l. Final evaluation of remission and response was made after 4 weeks of lithium addition.

Results: Since only 15 patients were included in phase II, evaluation of the two-phase treatment strategies was impossible, and lithium addition was evaluated as an open study. Lithium addition appeared remarkably effective, since 9 of 15 (60%) attained remission, defined as a final Hamilton Depression Rating Scale (HAM-D) score ≤ 7. The same number of patients achieved response (HAM-D reduction ≥ 50%). All 9 remitters had a sustained remission during a four-month follow-up period.

Conclusion: Lithium addition appears to be remarkably effective in psychotic depression, but these data from an open study are insufficient evidence for this treatment to be considered evidence based.

Trial registration: http://www.controlled-trials.com/isrctn/trial ISRCTN36607067
**Introduction**

Psychotic depression, in which delusions and/or hallucinations appear in the context of an episode of a major depressive disorder, is the most severe form of depression. Compared to non-psychotic depression, psychotic depression is more severe and more incapacitating, with longer duration of episodes, and more recurrence of psychotic features in subsequent episodes while it has a lower likelihood of placebo response.\(^1\) Up to 20% of patients with a major depressive episode meet criteria for psychotic depression.\(^2,3\) Electroconvulsive therapy (ECT) is often considered the most effective treatment for psychotic depression but pharmacotherapy may also be regarded as a suitable treatment option. The most appropriate pharmacotherapy for psychotic depression has been the topic of an ongoing controversy. Most studies report that patients suffering from psychotic depression respond poorly to antidepressant monotherapy.\(^2,4\) Most guidelines recommend the combination of an antidepressant plus an antipsychotic as first-choice treatment although a meta-analysis found no proof for better efficacy for the combination compared with antidepressant monotherapy, but only versus antipsychotic monotherapy.\(^5\) For patients with non-psychotic depression not responding to antidepressants, addition of lithium to ongoing treatment with antidepressants is probably the best-studied next step. In placebo-controlled studies in mostly non-psychotic depressed patients 42% responded to the addition of lithium versus 17% to placebo.\(^6\)

Despite suggestions that lithium addition might also be useful in patients with psychotic depression\(^7,8,9\) evidence for its effectiveness is still very limited. In the review by Wheeler Vega et al.\(^4\) lithium augmentation is mentioned as “a valuable second-line treatment for psychotic depression” without reviewing the evidence. In a retrospective study comparing psychotic depressed patients with patients with non-psychotic depression, Bruijn et al.\(^7\) found that 13 of 15 (87%) of psychotic depressed patients treated with imipramine and subsequent lithium addition achieved response.

Since relapse after successful ECT is a major problem, there clearly is a need to investigate pharmacological treatment strategies for psychotic depression, and lithium addition may prove to be an effective strategy for patients with insufficient response to antidepressants.

**Aim of the study**

The present study was aimed to compare imipramine, venlafaxine, and venlafaxine plus quetiapine (phase I), followed by lithium addition (phase II) for patients without response to the treatment in phase I. The results of the phase I study comparing the efficacy of imipramine, venlafaxine and a venlafaxine-quetiapine combina-
tion are presented elsewhere (Wijkstra et al., in press). The present report focuses on attaining remission during this two-phase treatment.

Method

Phase I: imipramine vs. venlafaxine vs. venlafaxine plus quetiapine (7 weeks)

The study presented here is the second phase of an investigator initiated (WAN), randomized, double-blind, controlled trial with eight participating centers in the Netherlands. Recruitment took place between June 2002 and June 2007. The protocol and the results of the first phase have been described elsewhere (Wijkstra et al., in press). In short, 122 hospitalized patients who met DSM-IV-TR criteria for major depression with psychotic features with a score ≥18 on the Hamilton Rating Scale for Depression-17 items (HAM-D)\(^{10}\) and who were without psychotropic medication for at least 4 days prior to the study, were randomized 1:1:1 to 7 weeks treatment with imipramine (dose adjusted to adequate plasma levels of 200-300 ng/ml\(^{11}\)), venlafaxine (maximum 375 mg/day) or venlafaxine plus quetiapine (maximum 375 mg/day/600 mg/day). As concomitant psychotropic medication, only benzodiazepines at a maximum of 3 mg lorazepam equivalent per day were allowed.

The study was approved by the ethical review board of the University Medical Center (UMC) Utrecht, and by the local review boards of the participating centers. All patients, or their legal relatives in case of incapacity, gave written informed consent prior to enrollment in the study. At baseline, diagnosis was confirmed with the Structured Clinical Interview for DSM-IV Axis I disorders.\(^{11}\)

Severity of depressive symptoms was assessed at baseline and then weekly using the HAM-D (17 items)\(^{10}\) and the Clinical Global Impressions (CGI)\(^{12}\) severity. In addition, all individual psychotic features (hallucinations or delusions, including whether they were mood-congruent or mood-incongruent) were documented at baseline and then weekly. Interrater reliability as indicated by the intraclass correlation coefficient and based on three patients and 8 raters was 0.93 (95%CI: 0.74-1.00) for the HAM-D total score.

Phase II: lithium addition (4 weeks)

For patients who did not attain response (HAM-D reduction ≥ 50% compared to baseline and final HAM-D ≤ 14) at the end of phase I, lithium was added for another 4 weeks. Patients entering phase II continued their blinded study medication at the same dose and lithium was started in an initial dose of 600 mg at 8.00 p.m. Serum
lithium levels (12 hours after the last evening dose) were measured on day 7 and weekly thereafter. Doses were adjusted to attain a lithium level of 0.6-1.0 mmol/l. Weekly assessments of the 17-item HAM-D, the CGI and psychotic features continued during phase II. As in phase I, the use of concomitant benzodiazepines, although permitted, was strongly discouraged and no more than 3 mg lorazepam equivalents were allowed.

After the 4-week study period, the code was broken in order to inform the clinician how to proceed treatment, but only after two weeks when all the data for that patient had been monitored and entered into the database. Another reason for unblinding was the practical impossibility of keeping patients on double-blind medication throughout the total duration of the study.

Two and four months after completion of phase II, patients had two follow-up visits to assess whether response and remission were sustained.

Data analysis

Our a priori purpose was to compare the efficacy of the three two-step treatment strategies with survival analysis by using the Cox proportional hazards model, using time to response as primary outcome criterion. However, since only 15 patients participated in phase II (lithium addition), this analysis appeared to be impossible. Therefore, the efficacy of lithium addition was calculated for all patients who received lithium addition, calculating remission (final HAM-D ≤ 7), response (HAM-D reduction ≥ 50% during phase II), and mean HAM-D reduction during phase II. Remission is considered the appropriate primary outcome criterion, since phase I followed by phase II requires a duration of pharmacotherapy of 11 weeks, and patients are treated with two (or even three) drugs during the final four weeks.

Furthermore remission is considered to be increasingly important as outcome measure. Adverse events were measured on a 4-point scale (none - light - moderate - severe) and were considered relevant if their severity was at least moderate and if they had increased compared with the last assessment prior to the addition of lithium.

Results

Unfortunately, it appeared to be difficult to enroll patients in this part (phase II) of the study. This was due to several causes: (1) fewer patients than anticipated participated in phase I; (2) the study protocol for phase II was completed substantially later than that for phase I, therefore approval from the ethical review board was obtained about 18 months after phase I was started; and (3) response rates after phase
I were somewhat higher than expected. During the 5-year study period of phase I, 122 patients were enrolled. Of the 122 patients who started and the 100 patients who completed phase I, 41 were nonresponders and were thus eligible for lithium addition (Figure 1).

**Figure 1** Flowchart of participation in the study
However, 26 of them did not enter phase II, most patients (n=16) because they had completed phase I prior to May 2003 (the initiation of phase II). Another four patients refused to take lithium, while three patients, although meeting criteria for nonresponse, appeared to have improved clinically on phase I study medication. Two patients were unblinded at the end of phase I, one because of worsening of psychotic symptoms, the other because of cardiovascular problems. One patient did not receive lithium addition for unknown reasons. Thus, the total study sample consisted of 15 patients: three patients using imipramine (mean dose 275 mg/day, range: 225-375 mg/day), seven patients using venlafaxine (all with a dose of 375 mg/day), and five on a venlafaxine plus quetiapine (all with a dose of 375 and 600 mg/day, respectively). Patients’ demographic and clinical characteristics at start of lithium addition (week 7) are summarized in Table 1.

Table 1  Demographic and clinical characteristics of patients receiving lithium addition

<table>
<thead>
<tr>
<th>Age, mean (range), y</th>
<th>53.9 (40-63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, N (%)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Number of previous episodes, mean±SD</td>
<td>1.0±1.6</td>
</tr>
<tr>
<td>Duration (weeks) of index episode, mean±SD</td>
<td>38.9±36.8</td>
</tr>
<tr>
<td>HAM-D score at the start of lithium addition, mean±SD</td>
<td>22.1±5.8</td>
</tr>
<tr>
<td>HAM-D score, after 4 weeks lithium treatment, mean±SD</td>
<td>9.1 ±8.0</td>
</tr>
<tr>
<td>With hallucinations, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>With delusions, n (%)</td>
<td>11 (73)</td>
</tr>
</tbody>
</table>

During the four-week study period none of the patients dropped out, during the subsequent 15 week follow-up three nonresponders discontinued medication: one because of side-effects, another due to protocol violation and a third because of worsening. All patients obtained a lithium serum level within the pre-defined therapeutic range with a mean serum level of 0.68 mmol/l (SD 0.14) at a mean dose of 840 (SD 445) mg/day. Eight of 15 (53%) patients used 1-3 mg lorazepam equivalent per day as concurrent medication during phase II. Psychotic features still were present in 11 of 15 patients at the start of phase II.

None of the patients experienced hallucinations at the start of phase II. Five patients showed delusions of guilt/sin, four patients had paranoid delusions, three suffered from delusions of poverty, three showed somatic delusions and three exhibited nihilistic delusions.
Efficacy

The mean HAM-D score decreased 13.0 points during the 4-week period of lithium addition.

After two weeks of lithium addition four patients had achieved response and two remission, at 3 weeks response was achieved by six patients and remission by four, by the end of the lithium addition phase, nine of 15 (60%) patients were responders and the same number of patients met criteria for remission. Table 2 gives the individual change in HAM-D score over time.

Table 2  Change in HAM-D score of patients during 4 weeks of lithium addition

<table>
<thead>
<tr>
<th>Patient no, Phase I medication</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 19 Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, imipramine</td>
<td>18</td>
<td>15</td>
<td>10</td>
<td>8(\dagger)</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>2, imipramine</td>
<td>17</td>
<td>17</td>
<td>14</td>
<td>13</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>3, imipramine</td>
<td>15</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>4, venlafaxine</td>
<td>36</td>
<td>20</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5, venlafaxine</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>20</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6, venlafaxine</td>
<td>25</td>
<td>27</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>7, venlafaxine</td>
<td>23</td>
<td>17</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>8, venlafaxine</td>
<td>26</td>
<td>29</td>
<td>27</td>
<td>26</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>9, venlafaxine</td>
<td>27</td>
<td>16</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>10, venlafaxine</td>
<td>23</td>
<td>18</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>11, venlafaxine+ quetiapine</td>
<td>24</td>
<td>20</td>
<td>18</td>
<td>17</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>12, venlafaxine+ quetiapine</td>
<td>14</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>13, venlafaxine+ quetiapine</td>
<td>27</td>
<td>16</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>14, venlafaxine+ quetiapine</td>
<td>20</td>
<td>20</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>15, venlafaxine+ quetiapine</td>
<td>16</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

\(\dagger\) figures in bold means that the criterion for response is met.

During the additional 15-week follow-up period all patients continued their study medication, which was unblinded. For all nine remitters at the end of 4 weeks lithium addition, their remission was sustained during the follow-up period.
Doses and serum levels

Three patients received imipramine, mean dose 275 mg (range: 225-375 mg), all seven patients on venlafaxine received 375 mg, five patients receiving combination treatment all used 375 mg venlafaxine and 600 mg quetiapine. Serum lithium levels are available for all 15 patients for whom lithium was started. The mean lithium level after the attainment of the target level was 0.68 mmol/liter (SD= 0.14). Three patients had a lithium level < 0.6 mmol/l on at least one occasion. Mean lithium dose after achieving the target level was 840 ± 445 mg (range: 400-1200 mg).

Adverse effects

Overall lithium was well tolerated. No patients dropped out due to side effects in the four weeks of phase 2, while only one patient in whom lithium was added to venlafaxine dropped out during follow-up (due to an allergic skin reaction). Compared to the last assessment prior to lithium addition, three patients experienced severe adverse events: two patients receiving venlafaxine and lithium complained of severe loss of libido and a severe tremor, and another patient receiving venlafaxine, quetiapine and lithium had a severe tremor and severe tiredness. Table 3 shows the exact frequencies of the specific adverse events.

Table 3  Adverse Effects (AEs) in patients receiving lithium addition compared to baseline

<table>
<thead>
<tr>
<th>Effect</th>
<th>No. of AEs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe tremor</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Moderate tremor</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Severe loss of libido</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Moderate loss of libido</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Severe tiredness</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Moderate dry mouth</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Moderate insomnia</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Moderate dizziness</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Moderate headache</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Moderate agitation</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Moderate myoclonus</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>
Discussion

With a planned number of 155 patients who would be included in phase I, an anticipated drop out rate of 20% in phase I, a response rate of 50% and another 15% drop outs before starting with lithium, we had anticipated to be able to include 46 patients in the second phase. However, we only succeeded in including 15 patients. Therefore, we did not achieve the purpose of our study: to compare the overall results of a two-step treatment strategy in psychotic depression with imipramine, venlafaxine, and venlafaxine plus quetiapine as first step followed by subsequent addition of lithium for patients with insufficient response.

Our aim and expectation was that we would include in phase II approximately 50% of the patients enrolled in phase I. This assumption was based on previous two-step treatment strategy studies in depressed inpatients\(^5\,^6\) whose sample consisted of both patients with psychotic depression (one-third) and patients with non-psychotic depression (two-thirds). In these studies, 57 of 107 (53%) and 71 of 138 (51%) patients who entered phase I, subsequently received lithium addition.

Because of the small number of patients receiving lithium addition we had to abandon our aim of comparing the efficacy of the three treatment strategies (i.e. imipramine and imipramine+ lithium versus venlafaxine and venlafaxine+ lithium versus venlafaxine-quetiapine and venlafaxine-quetiapine+ lithium). We now consider phase II (lithium addition) of our study as an open study. Our main finding is that the majority of patients (60%) of patients who had not responded to the first pharmacological treatment step (either monotherapy with an antidepressant or combination therapy with an antidepressant plus an antipsychotic) did respond to addition of lithium. As there was no placebo arm in our study, our findings suggest but do not proof that addition of lithium is effective as a subsequent treatment step for patients with psychotic depression not having responded to an antidepressant (with or without an antipsychotic), as has been proven for patients with non-psychotic depression who have not responded to an antidepressant.\(^5\)

The pharmacological treatment of psychotic depression is severely understudied and especially the treatment of patients who have not responded to a first step with either antidepressant monotherapy or the combination of an antidepressant with an antipsychotic. A possible explanation for this is that patients with psychotic depression are relatively rare, about 30% of depressed inpatients show psychotic features. Furthermore, if patients are severely ill (e.g. refusing food and fluids) there is a need for acute electroconvulsive therapy.

In addition, because many psychotic depressives blame themselves for their current state and do not consider themselves to be ill, they could not give informed consent to a study, so often informed consent will have to be obtained from a close relative.
To our knowledge there are no previous studies on lithium addition in a population of antidepressant-refractory patients with psychotic depression. Therefore, we consider our findings with impressive response and remission rates of 60% – although resulting from an open, uncontrolled study - of high clinical relevance.

We consider it unlikely that our positive results can be explained by a placebo response, since the response to placebo is considered to be very low in psychotic depression. Furthermore, the sustaining remission during the 15-week follow-up period also argues against a response due to non-specific factors. Moreover, all patients in our study had already participated in a 7-week study (phase I) prior to the current study (phase II), which they had completed as non-responders. Another possible explanation for our positive finding is a delayed response to the medication of phase I, but given the fact that the mean HAM-D scores of the patients in our study had improved only 9.8 points during phase I compared to 13.0 points in phase II, and that most improvement in phase II did not occur in the first week (3.6 points) but in the last three weeks (9.4 points) we consider this a rather unlikely explanation. The efficacy of lithium addition can be evaluated properly only if treatment with the antidepressant, including dosing, in the first phase is optimal. Optimal antidepressant treatment was achieved in the first phase of the study (Wijkstra et al, in press).

As in the present study the effect of lithium addition gradually appeared between week 2 and 4, this raises the question whether a 4-week treatment period is optimal for this strategy. The apparent lack of fast (within 1 week) response to lithium addition is not in accordance with previously published case series in patients with psychotic depression, in which response was achieved within one week by 2 of 5 patients and 2 of 6 patients, respectively. The combination of lithium with high doses of venlafaxine was tolerated well with no indication for a substantial risk of a serotonin syndrome described previously during venlafaxine-lithium treatment.

In conclusion, although our data suggest that lithium addition is an effective subsequent and well tolerated step in the pharmacological treatment for patients with psychotic depression, larger controlled studies of lithium addition in psychotic depression are warranted, but our study also clearly shows the difficulties, which can be encountered when performing such a study in psychotic depressed patients.
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