Lithium Augmentation Compared With Phenelzine in Treatment-Resistant Depression in the Elderly: An Open, Randomized, Controlled Trial

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Background: Up to a third of elderly patients with major depressive disorder do not respond to a first course of treatment with an antidepressant. There is a lack of controlled studies evaluating therapies for treatment-resistant depression in late-life depression, and no randomized controlled studies assessing the efficacy and tolerability of lithium augmentation in elderly patients have been published.

Method: Twenty-nine elderly inpatients with major depressive disorder according to DSM-IV criteria who had previously failed to respond to 1 or more adequate trials with a tricyclic antidepressant or venlafaxine were included in a 6-week, open, randomized, controlled study with a 2-year follow-up. Subjects received either lithium augmentation or the monoamine oxidase inhibitor phenelzine. The primary outcome criterion was remission, defined as a final score of less than or equal to 10 on the Montgomery-Asberg Depression Rating Scale (MADRS). Response was defined as at least 50% reduction on the MADRS or the Hamilton Rating Scale for Depression (HAM-D).

Results: Twenty-eight subjects completed the trial. Remission on the MADRS was achieved by 33.3% of the lithium patients, compared with none of the phenelzine patients ($p = .042$). Response also showed a difference in favor of lithium augmentation ($p = .035$ on both the MADRS and the HAM-D). Overall tolerability was good, with no dropouts due to side effects. Subjective memory impairment was more prevalent among patients receiving phenelzine ($p = .002$), and tremors were significantly more prevalent among patients receiving lithium ($p = .002$). During the 2-year follow-up, 25 patients (86.2%) did achieve remission, particularly on prolonging the lithium treatment (5 patients) or on lithium augmentation to phenelzine (5 patients).

Conclusion: Lithium was more effective than phenelzine in elderly patients with treatment-resistant major depressive disorder, while tolerance of both treatments was remarkably good in this group of elderly inpatients with many comorbid medical disorders.

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Depression in the elderly is a prevalent condition, which contributes to personal suffering and increased disability, mortality, suicide risk, and health care utilization.[1]

Many treatments of depression in the elderly can be effective, such as pharmacotherapy, psychosocial therapies, and electroconvulsive therapy (ECT).[1] However, clinical experience and the limited published data indicate that up to a third of elderly patients with major depression do not respond to treatment. Determining the exact prevalence of treatment-resistant depression (TRD) is difficult because the definition is highly variable and there is no validated definition.[2] The World Psychiatric Association (WPA) defined TRD as an absence of clinical response to treatment with a tricyclic antidepressant at a minimum dose of 150 mg/day of imipramine (or equivalent drug) for 4 to 6 weeks.[3] With TRD defined closely to the WPA definition, a recent systematic review of pharmacologic and psychological interventions in adults aged 18 to 75 years identified 17 randomized controlled trials (RCTs).[4]

Besides ECT, several major options remain for patients with TRD, including lithium augmentation (the addition

of lithium to ongoing treatment with an antidepressant) and switching to an irreversible monoamine oxidase inhibitor (MAOI). Lithium augmentation is probably the option with the best evidence with, according to a meta-analysis of 10 placebo-controlled studies, a number needed to treat of only 3.7.[5] Monoamine oxidase inhibitors have not been compared with placebo, but have been shown to be as or even more effective than other treatments with response rates of around 50% (range, 38%–73%).[6–11]

At present, published RCTs in exclusively elderly patients (mean age ≥ 60 years) with TRD investigated mainly nonpharmacologic strategies, namely ECT or rapid transcranial magnetic stimulation.[12–14] The only double-blind RCT evaluating pharmacotherapy in elderly patients with TRD found the MAOI selegiline to be more effective than placebo in 16 patients aged 55 years and older.[15] All other pharmacotherapy studies in the elderly are uncontrolled studies. In the largest prospective study published to date, 57.5% of 40 depressed patients, who were refractory to or intolerant of an initial trial of nortriptyline, responded to another antidepressant.[16] In a more recent, combined publication of 2 separate uncontrolled studies among 65 patients, 60% responded to augmentation strategies using bupropion, nortriptyline, or lithium, compared with a response rate of 42% after switching to venlafaxine.[17] Lithium augmentation has been studied in 5 uncontrolled studies involving a total of 77 patients.[16,18–21] Four of these trials[16,18,19,21] used a final score of less than or equal to 7 to 10 on the Hamilton Rating Scale for Depression (HAM-D) as outcome criterion and found that 25 of 72 patients (34.7%) achieved remission. Although detailed information about dropouts is not given in all studies, at least 3 patients dropped out due to side effects, and in one other patient, the dose of lithium had to be decreased due to side effects.

The effect of MAOIs has also been studied in 1 controlled and 5 uncontrolled studies involving 95 elderly patients.[15,18,22–25] The combined response rate (defined as ≥ 50% decrease in HAM-D score) in these studies was 40% (12 of 30 patients), and the remission rate (defined as a HAM-D score of ≤ 10 or 11) was 55% (28 of 51 patients). Twelve patients dropped out due to side effects, and in 2 other patients, the dose had to be decreased due to side effects.

The objective of this study is to compare the efficacy and tolerability of lithium augmentation versus the classical MAOI phenelzine in the treatment of elderly inpatients with major depressive disorder nonresponsive to previous adequate treatment with a tricyclic antidepressant (TCA) or with venlafaxine extended release (XR). On the basis of prior clinical experience and our review of the literature above, we expected that the efficacy of both medications would not be different. Moreover, we expected that phenelzine might be better tolerated than lithium.

METHOD

Subjects

Our study was an open, randomized, controlled trial with 2 treatment arms: lithium augmentation and switch to phenelzine. A double-blind trial was not deemed feasible as the lithium serum level had to be monitored in the lithium-treated patients, dietary restrictions were necessary for the phenelzine patients, and the antidepressant had to be continued in the lithium patients and stopped in the phenelzine patients.

Patients were recruited from 1 psychiatric hospital between January 2000 and December 2004. Patients with a minimum age of 60 years were diagnosed by the first author (R.M.K.) and had to meet the DSM-IV criteria for major depressive disorder, confirmed with the International Diagnostic Check List,[26] and a baseline score of greater than or equal to 20 on the Montgomery-Asberg Depression Rating Scale (MADRS).[27] They all had not responded to at least 1 treatment with a TCA (minimal 4 weeks with serum levels within the therapeutic window) or venlafaxine XR (minimal 4 weeks with a minimum dose of 150 mg/day or a sum serum level of venlafaxine + O-desmethylvenlafaxine > 200 μg) during the current episode. Exclusion criteria were the use of either lithium or phenelzine in the current episode, use of any psychotropic drug that could seriously interact with phenelzine or lithium, a Mini-Mental State Examination (MMSE)[28] score of less than 15, meeting DSM-IV criteria for dementia or a nonaffective psychotic disorder, a history of bipolar disorder, abuse of alcohol or drugs within the last 2 years, and any physical illness that could seriously interact with treatment with either lithium or phenelzine.

This trial was conducted in accordance with the Declaration of Helsinki (1964), as amended in Edinburgh (2000), and has been approved by the ethical review committee of our hospital. Written informed consent was obtained from all patients or (in case of incompetence) from their legal representative before study entry.

Treatment

Patients were randomly assigned by computer in a 4 × 2 block design to receive lithium augmentation or phenelzine for 6 weeks. Sealed opaque envelopes containing the randomization numbers were used for concealment of allocation.

Patients receiving lithium augmentation continued the antidepressant (TCA or venlafaxine XR) to which they had not responded before in the same dose. Lithium was given as lithium carbonate in 1 dose in the evening, starting with 200 mg/day and further titrated to obtain plasma

levels of 0.6 to 1.2 mmol/L. Patients receiving phenelzine had the antidepressant tapered down over 1 to 2 weeks and were without any antidepressant for at least 3 days prior to the start of phenelzine. Phenelzine was given in 1 or 2 doses at 8:00 a.m. and 12:00 a.m., starting with 15 mg/day for the first 3 days, then increased to 30 mg/day at days 4 through 8, and further increased in weeks 3 through 6 with 15 mg/week to a maximum of 60 mg/day based on tolerability and clinical response. Despite the different lead-ins, both arms lasted 6 weeks starting from the first administration of the drug.

As elderly patients frequently use comedications, we allowed oxazepam with a maximum of 50 mg/day, temazepam with a maximum of 20 mg/day, haloperidol with a maximum of 5 mg/day, and risperidone with a maximum of 2 mg/day (all psychotic patients received an antipsychotic). Doses were kept stable when possible during the study period, as was medication for physical illnesses.

After completion of the trial, patients entered a 2-year follow-up, during which decisions about dosing or changing of antidepressants were made according to the following treatment protocol: switching to nortriptyline after unsuccessful lithium augmentation to venlafaxine, switching to phenelzine after unsuccessful lithium augmentation to nortriptyline, lithium augmentation after unsuccessful treatment with phenelzine, and ECT for patients not responding to any of the steps above (or earlier in case of psychotic depression).

Assessments

Prior to the study, a composite antidepressant treatment score was calculated for the "best" treatment during the current episode using the Antidepressant Treatment History Form (ATHF).[29] For staging the overall treatment resistance, the Massachusetts General Hospital staging method was used to generate a continuous score that considers both number of trials and intensity and optimization of each trial.[30]

The severity and disability of the medical comorbidity was quantified according to Burvill et al.[31] using information from the patient's history and physical examination and from review of the medical records obtained from the primary care physician.

Assessments of efficacy and tolerability were performed by an independent interviewer (D.V.), a trained psychologist who was blind to the study medication. Efficacy was assessed at baseline and at weeks 3 and 6 with the MADRS, the 17-item HAM-D,[32] the 30-item Geriatric Depression Scale (GDS),[33] and the Clinical Global Impressions-Improvement scale (CGI-I).[34]

The primary efficacy outcome criterion was remission, defined a priori as a final score of less than or equal to 10 on the MADRS. Secondary efficacy outcome criteria were remission on the HAM-D (score ≤ 7) and GDS (score ≤ 10) and response defined as a reduction of at least 50% of scores on the MADRS, HAM-D, and GDS or a CGI-I score of 1 (very much improved) or 2 (much improved).

Safety was assessed with the Symptoms, Sign, Side-Effect Checklist (SES),[35] evaluating the presence and severity of 43 symptoms or side effects at baseline and in weeks 1, 2, 4, and 6. The SES also requires an indication of the rater's judgment of the relationship between the side effect and the drug and any action undertaken as a consequence of its presence. Cognitive functioning was evaluated with the Dutch version of the California Verbal Learning Test (CVLT)[36] and the Trail-Making Test (TMT)[37] (both assessments were made by trained psychologists at baseline and at week 6). Laboratory evaluations (at baseline and at week 6) and electrocardiograms (ECGs measuring PQ interval, QRS complex, or QTc interval at baseline and at week 6) were also analyzed as safety variables. Study events and vital signs (heart frequency and blood pressure) were monitored every week. Orthostatic hypotension was defined as a fall of greater than or equal to 20 mg Hg in systolic blood pressure or greater than or equal to 10 mg Hg in diastolic blood pressure within 3 minutes of standing after the patient had rested for at least 5 minutes in a supine position.

The primary safety outcome measure was the investigators' overall clinical assessment of tolerance, an ordered categorical variable (1 = no side effects, 2 = minimal side effects, 3 = moderate side effects, 4 = serious side effects, 5 = trial stopped because of side effects).

During the 2-year follow-up, patients were assessed by the first author (R.M.K.) using the MADRS, HAM-D, GDS, CGI-I, and SES 6, 9, 12, 24, and 36 months after starting the trial.

Statistical Analysis

Efficacy and safety measures were analyzed in the intention-to-treat sample, which was defined as all patients who were randomly assigned to treatment. The assumptions of normality and homogeneity of variance were assessed by inspection of normal probability plots. The 2 treatment groups were analyzed for comparability at baseline with the t test for continuous variables with a normal distribution, with the χ^2 test for categorical measures, and with the Mann-Whitney test for nonparametric data.

The treatment groups were compared with paired sample t tests for continuous efficacy variables with a normal distribution (MADRS, HAM-D, and GDS) and with the χ^2 test and Fisher exact test for the CGI-I scores and individual side effects on the SES. All comparisons were made with SPSS 12.0 for Windows (SPSS, Inc., Chicago, Ill.) using 2-sided tests and are presented as p values. To correct for multiple testing, a p value of less than or equal to .01 was considered significant for all post hoc–defined secondary outcome variables.

Figure 1. CONSORT Diagram of Trial Participants

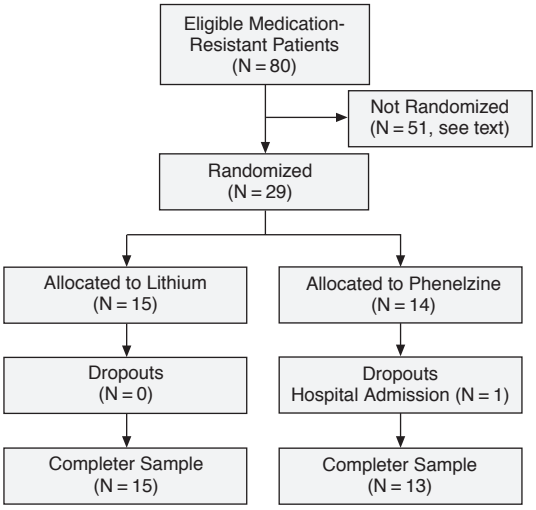

Table 1. Demographic and Clinical Characteristics at Baseline of 29 Randomly Assigned Elderly Patients (intention-to-treat group)

Characteristic	Lithium (N = 15)	Phenelzine (N = 14)	p
Age, mean (SD), y	73.6 (7.3)	72.6 (7.7)	.715
Female, N (%)	11 (73.3)	11 (78.6)	1.0
Single episode, N (%)	5 (33.3)	1 (7.1)	.169
Late-onset depression, N (%)[a]	10 (66.6)	6 (42.9)	.198
Psychotic features, N (%)	7 (46.7)	11 (78.6)	.077
Melancholic features, N (%)	14 (93.3)	12 (85.7)	.210
Duration of index episode, mean (SD), mo	11.7 (13.5)	7.4 (3.4)	.250
No. of used antidepressants for index episode, mean (SD)	1.9 (1.3)	1.7 (0.7)	.693
ATHF best treatment score, mean (SD)	3.6 (0.5)	3.6 (0.6)	.895
MGH overall staging score, mean (SD)	2.1 (1.1)	2.2 (1.1)	.719
No. of concomitant psychiatric medications, mean (SD)	2.0 (0.4)	2.0 (0.9)	1.0
No. of concomitant medical diagnoses, mean (SD)	5.1 (2.3)	3.8 (2.5)	.165
No. of concomitant somatic medications, mean (SD)	4.8 (2.1)	3.3 (1.4)	.032
MMSE score, mean (SD)	25.9 (3.6)	27.0 (2.0)	.358

[a]First episode after age 60 years.
Abbreviations: ATHF = Antidepressant Treatment History Form, MGH = Massachusetts General Hospital, MMSE = Mini-Mental State Examination.

RESULTS

During the recruitment period (2000–2004), 188 elderly inpatients with major depressive disorder were admitted to our hospital. Fifty-three patients (26.6%) responded to the first antidepressant, and 55 patients (29.3%) responded to a subsequent trial of a TCA or venlafaxine, leaving 80 patients (42.6%) who did not respond to an adequate trial (see study procedures) of a TCA or venlafaxine (Figure 1). Of these, 51 (63.8%) were not included; 7 patients already used lithium at the time of admission, 7 patients were demented, 11 patients had a MADRS score of less than 20, 5 patients refused, 7 patients were discharged before they could participate in the trial, 3 patients had serious contraindications or side effects to nortriptyline, 2 patients were given ECT, 7 patients were excluded because the treating physician refused random assignment due to a preference for treating with lithium, and 2 patients were missed due to administration failures. The 51 patients who were not included did not differ from the 29 included patients in age, gender, and mean score on the MADRS, GDS, or MMSE (other variables not available).

The characteristics of the included patients are summarized in Table 1. All 29 patients received the allocated intervention: 15 received lithium augmentation and 14 received phenelzine. There were no significant between-group differences. According to the rating of the severity and disability of the physical illnesses by Burvill et al,[31] in 14 patients, the severity of the physical illness was moderate or severe, and 11 patients had at least some kind of physical disability. The study population can be characterized as elderly inpatients with a recurrent, severe, treatment-resistant depression and moderate-severe physical illnesses.

The majority of patients (62% [N = 18]) had not responded to at least 2 previous treatments with antidepressants. All patients had a score of 3 or 4 for the most adequate treatment episode according to the ATHF, except for 1 patient with a score of 2. According to the Massachusetts General Hospital staging method, the mean overall score for the previous treatments was 2.2 (SD = 1.1).

At baseline, all but 1 of the 29 patients were taking psychotropic medication: 17 were taking an antipsychotic, 17 an anxiolytic agent, and 20 a hypnotic agent. During the trial, the dosages were changed in 6 cases (all increased; in 2 lithium-treated patients and 4 phenelzine-treated patients), and in 7 cases, the medication was stopped (all but 1 were treated with phenelzine). In addition, 3 patients started with an antipsychotic during the trial and 3 patients with a hypnotic (all of these patients took phenelzine). Mean maximum daily doses for patients using these medications were haloperidol 2.2 (SD = 1.5) mg, risperidone 1.8 (SD = 1.3) mg, oxazepam 24 (SD = 9) mg, and temazepam 18 (SD = 9) mg. There were no statistically significant differences in dosages of concurrent psychotropic medications or in number of patients using them between both treatment groups.

Lithium was augmented in 12 patients to nortriptyline (mean dose of 90 [SD = 41] mg/day and a mean plasma level of 124 [SD = 33] ng/mL) and in 3 patients to venlafaxine XR (all 3 took 225 mg/day). At endpoint, the mean dose of lithium was 527 (SD = 96) mg/day with a range of 400 to 600 mg/day, and the mean final plasma level was

Table 2. Efficacy Results of Elderly Patients (intention-to-treat group)[a]

Measure	Lithium (N = 15)	Phenelzine (N = 14)	p
MADRS baseline score, mean (SD)	32.1 (5.8)	33.0 (6.2)	.677
MADRS endpoint score, mean (SD)	19.0 (11.8)	33.4 (11.1)	.003
Remission on MADRS, N (%)[b]	5 (33.3)	0 (0)	.042
Response on MADRS, N (%)	7 (46.7)	1 (7.1)	.035
HAM-D baseline score, mean (SD)	22.7 (3.0)	22.1 (5.4)	.722
HAM-D endpoint score, mean (SD)	12.7 (7.9)	21.5 (6.4)	.004
Remission on HAM-D, N (%)	5 (33.3)	0 (0)	.042
Response on HAM-D, N (%)	7 (46.7)	1 (7.1)	.035
GDS baseline score, mean (SD)	23.5 (4.2)	24.5 (4.7)	.574
GDS endpoint score, mean (SD)	16.9 (9.6)	22.7 (7.8)	.105
Remission on GDS, N (%)	5 (33.3)	1 (7.1)	.182
Response on GDS, N (%)	4 (26.7)	1 (7.1)	.356
CGI-I score 1–2, N (%)	8 (53.3)	2 (14.3)	.050

[a]For all analyses, N = 29, except for MADRS/HAM-D endpoint (N = 28), GDS remission/GDS endpoint scores (N = 27), and GDS response score (N = 26).
[b]Primary outcome criterion.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, GDS = 30-item Geriatric Depression Scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Clinical Assessment of Tolerability Scores for Elderly Patients (intention-to-treat group)

Clinical Assessment of Tolerability Score	Lithium (N = 15)	Phenelzine (N = 14)
No side effects	1	0
Minimal side effects	10	8
Moderate side effects	4	6
Serious side effects (leading to dropout)	0	0

0.71 (SD = 0.17) mmol/L. All patients had a lithium serum level between 0.6 and 1.2 mmol/L at endpoint, except for 2 patients with lower serum levels; in these patients, side effects (1 patient with severe edema and 1 patient with a tremor) prevented dose increase. At endpoint, patients taking phenelzine used a mean of 46 (SD = 9) mg/day with a range of 30 to 60 mg/day, but only 3 patients used the allowed maximum of 60 mg/day. Two patients used 30 mg/day; in both patients, side effects prevented dose increase (1 patient with orthostatic hypotension and 1 patient with both orthostatic hypotension and worsening of cognitive functions).

One patient treated with phenelzine dropped out during the trial as a result of hospitalization due to pneumonia in week 5. At week 3 and week 6, assessments of this patient suggested worsening of the depression, and she is considered a nonresponder in the intention-to-treat analysis.

Efficacy

Primary and secondary outcome variables in the intention-to-treat group are presented in Table 2. Remission, defined as a final score on the MADRS of 10 or less (the primary efficacy outcome criterion), was achieved in 5 of 15 patients receiving lithium augmentation and in none of the 14 patients receiving phenelzine (p = .042). On the secondary outcome measures, there was also a statistically significant difference between patients with lithium and phenelzine in achieving remission on the HAM-D (the same patients), in having a response on the MADRS and the HAM-D, and in a final CGI-I score of 1 to 2.

Patients who were given lithium achieved a mean reduction at endpoint of 13.1 (SD = 8.9) on their MADRS score (p < .001), of 10.0 (SD = 6.3) on their HAM-D score (p < .001), and 6.6 (SD = 9.6) on their GDS score (p = .018). Patients who were treated with phenelzine achieved a mean increase at endpoint of 0.7 (SD = 12.8) on their MADRS score (p = .849), an increase of 0.1 (SD = 7.8) on their HAM-D score (p = .972), and a reduction of 1.7 (SD = 10.2) on their GDS score (p = .588).

Psychotic patients had a clinically meaningful, although not statistically significantly different, lower mean reduction in MADRS score compared with nonpsychotic patients (3.7 [SD = 13.7] and 11.5 [SD = 10.1], respectively, p = .116).

Tolerability

All but 1 patient (treated with phenelzine) experienced at least 1 adverse event. Patients treated with lithium reported a mean number of 4.3 (SD = 2.8) side effects compared with a mean number of 5.7 (SD = 3.7) reported by phenelzine-treated patients (p = .264). Side effects were usually mild or moderate in intensity, with 33.8% of all patients requiring some kind of action. In 2 patients treated with lithium, the dose was decreased because of too high serum levels; in 2 other patients, due to side effects, increase in dose was prevented despite levels lower than 0.6 mmol/L (see above). In the phenelzine group, the dose was decreased temporarily in 1 patient and in another patient could not be increased to 45 mg/day because of side effects.

As mentioned before, no subjects had to be withdrawn from treatment by the attending physician due to side effects. The overall Clinical Assessment of Tolerability score at endpoint is shown in Table 3; this score did not differ between the treatment groups (p = .452).

Table 4 shows the most frequent side effects in the 2 treatment groups. The only side effects revealing a significant difference were memory impairment, which was more prevalent among patients receiving phenelzine, and tremors, which was more prevalent among patients receiving lithium.

At baseline, there were no differences between the 2 treatment groups in cognitive functioning according to scores on the CVLT and the TMT, but the scores on the TMT suggest that the majority of patients did have sig-

Table 4. Side Effects Reported by Elderly Patients (reported in at least 10% of all patients)

Side Effect	Lithium, N (N = 15)	Phenelzine, N (N = 14)	p
Anxiety, nervousness	1	3	.33
Excitement, agitation	0	3	.1
Insomnia	2	8	.021
Weakness/fatigue	3	8	.039
Memory impairment	0	7	.002
Increased appetite	2	1	1.0
Headache	2	1	1.0
Tremors	12	3	.002
Rigidity, stiffness	1	3	.33
Akathisia	1	3	.33
Dystonia	2	1	1.0
Blurred vision	2	4	.39
Dry mouth	5	8	.198
Nausea, vomiting	3	3	1.0
Diarrhea	2	1	1.0
Constipation	3	4	.682
Syncope/dizziness	4	6	.45
Impaired urination	3	3	1.0
Weight gain	5	2	.39

nificant cognitive dysfunctions at baseline. In both treatment groups, no significant changes were found in CVLT and TMT scores during treatment.

In 1 patient, it was not possible to test for orthostatic hypotension at baseline. In the remaining 28 patients, the prevalence of orthostatic hypotension decreased during treatment from 68% at baseline to 38% at the end of the trial. There were no statistically significant differences between the treatment groups in either the number of patients having orthostatic hypotension or in the mean systolic or diastolic fall in blood pressure at standing at any visit.

There were also no statistically significant differences before and after treatment in heart frequencies, ECG parameters, or laboratory evaluations in the treatment groups. No patients developed a clinically relevant change in heart frequency or in any ECG or laboratory parameters.

Follow-Up Phase

In the lithium group, 9 of the 10 patients not in remission after 6 weeks did remit (all within the next 6 months), and 1 patient never reached remission criteria. Of these 9 patients, 5 remitted during continuation of the lithium, 1 after switching to nortriptyline, 1 after switching to phenelzine, 1 on lithium augmentation after unsuccessful switching to nortriptyline, and 1 with ECT after unsuccessful switching to phenelzine. Two patients died during the follow-up period; both were in complete remission and still used nortriptyline and 1 patient also still used lithium.

In the phenelzine group, 11 of the 14 patients not in remission after 6 weeks finally reached remission criteria but only 6 within the next 6 months and the other 5 in the 6 months thereafter. Three patients never reached remission criteria; 1 patient died taking phenelzine and lithium after a hip fracture a few months after finishing the trial, 1 patient developed dementia and was discharged at his families' request before remission was achieved, and 1 patient was transferred to a long-stay ward. Of the 11 patients reaching remission during follow-up, 2 patients did so during continuation of phenelzine, 5 patients during lithium augmentation to phenelzine, 2 patients during lithium augmentation after unsuccessful switching to a TCA, and 2 patients during ECT. During the follow-up, 2 other patients died who still used phenelzine, both were in complete remission.

During follow-up, 1 patient had to stop phenelzine as a result of a serious elevation of hepatic enzyme levels, and 1 patient had to start thyroid hormone therapy due to lithium-induced hypothyroidism.

DISCUSSION

There is a paucity of studies in late-life treatment-resistant depression. To our knowledge, our study is the first published RCT on the effects of lithium augmentation in this particular patient group. In our study, the overall efficacy was modest with only 5 patients (17.2%) meeting our primary outcome criterion of remission on the MADRS and 8 patients (27.6%) having a response. Various reasons may explain these overall low remission and response rates.

First, we may have selected a group of patients with a more advanced stage of treatment-resistant depression than other trials mentioned before. The majority of the patients (62%) had not responded to at least 2 antidepressants, and all but 1 patient had a score of 3 or 4 for the most adequate treatment episode according to the ATHF. All other trials with lithium augmentation or phenelzine in the elderly are at least 10 years old and were published without detailed information about the adequacy of previous trials to which patients had not responded. If information is presented, many trials can be criticized for their short trial duration (e.g., Uehlinger et al.[20] and Zimmer et al.[21] had a trial duration of only 4 weeks) or for the low serum levels allowed of nortriptyline. Of the 5 trials using nortriptyline as the gold standard, only Reynolds et al.[19] used a higher minimum serum level of 80 mg/mL instead of the usual 50 mg/mL, which may be too low in many treatment-resistant patients. Flint and Rifat[18] also included patients who did not respond to fluoxetine (mean dose of 35 mg) and phenelzine (mean dose of 53 mg) in their study. So, perhaps our lower efficacy rates may be explained by a higher stage of treatment resistance.

Second, another important difference between our trial and all other studies is that 62% of our study population has psychotic features, a well-known predictor of

nonresponse. In other prospective TRD studies in the elderly, patients with psychotic features were excluded[16,19] or specific information about psychotic patients is lacking. In adult TRD patients treated with an MAOI, only 1 recent study presents data on psychotic patients, and this had no influence on response.[10] In our trial, psychotic patients had a clinically meaningful lower reduction of MADRS score than the nonpsychotic patients, although this difference was not statistically significant, perhaps due to small subgroups.

Third, elderly patients also have many medical comorbidities, another established predictor of nonresponse.[38] Unfortunately, almost none of the other trials on TRD in the elderly present data on medical comorbidities, so we can only speculate if this also plays a role in our poor short-term treatment results. As the lithium group had a better outcome and also had a higher mean number of concomitant medical diagnoses and concomitant somatic medications than the phenelzine group, and remitted patients did not differ significantly from nonremitted patients in these 2 variables, it is not likely that the medical comorbidities explain our low efficacy rates.

Fourth, the duration of the trial may not have been optimal, as some elderly patients may have a slower response to treatment than their younger counterparts, although the 6-week duration of our trial is longer than most other trials of TRD in the elderly. In the prospective open studies with lithium augmentation, trial duration was usually 2 to 3 weeks. Only 1 study allowed patients to continue until they received the study criterion for response, which was usually after 4 to 6 weeks.[18] In the open trials with phenelzine in the elderly, trial duration was usually 3 to 6 weeks, with 1 study allowing 2 to 7 weeks.[23]

Our study found an important difference between the brittle short-term efficacy and the more optimistic long-term efficacy, as most patients (86.2% [N = 25]) eventually did respond to vigorous systematic treatment. Our results confirm those of Flint and Rifat,[18] who found that 83.2% of 101 elderly patients responded to a sequential antidepressant treatment with nortriptyline, lithium, phenelzine, or ECT.

An unexpected but important finding of our study is that lithium augmentation was significantly more effective than switching to phenelzine, as indicated by the number of patients achieving remission. In the lithium group, 5 patients (33%) met the primary outcome criterion of remission, and 7 patients (46.7%) responded. This effect is comparable with the remission rate of 34.7% according to uncontrolled trials in the elderly mentioned in the introduction, while the response rate is comparable with the mean response rate of 45% in younger adults.[5] Lithium augmentation is the most rigorously studied strategy in TRD in adults, and our study is the first RCT to confirm this in a group of elderly patients.

The effect of phenelzine in our study was unexpectedly low: no patient achieved remission and only 1 patient (7.1%) responded. This is remarkably lower than the results of both uncontrolled trials with MAOIs in the elderly and the RCTs in adult patients (see introduction). The poor results of phenelzine may be explained by various reasons.

First, the adequacy of the dose of phenelzine in our study (mean of 46 mg/day) may be questioned. A recent RCT comparing tranylcypromine with phenelzine in adults with TRD used a relatively high daily dose of phenelzine (mean of 79 mg) and found remission and response rates of 11% and 47%, respectively.[10] In this trial, tranylcypromine had a remission rate of 18% obtained with 60.5 mg/day among inpatients compared with lower remission rates (6.9%) in the U.S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial among outpatients using a relatively low mean dose of 36.9 mg/day.[6] Also, the STAR*D trial has been discussed regarding its too low dose of tranylcypromine.[39]

In the prospective open trials in the elderly, the dose of phenelzine differed from 15 to 75 mg/day, and textbook dose recommendations vary from 15 to 60 mg/day to 30 to 45 mg/day.[40,41] Only 1 study in the elderly reported the actual received maximum dose of phenelzine (mean = 49.5 mg/day [SD = 16 mg/day],[24] very similar to our study), and in that study, 65% of the patients achieved remission. Nevertheless, we cannot rule out the possibility that the low dosages of phenelzine may explain its low efficacy in our study.

Second, the duration of the study may have been too short, especially for phenelzine. As in adults, lithium is often efficacious within 2 to 3 weeks[5]; this may be faster than the response with an MAOI, leaving the possibility that trials of short duration (< 3 weeks) favor lithium augmentation to an MAOI. Moreover, lithium was immediately added to an antidepressant, while the phenelzine group first received a washout over 2 weeks prior to start of the medication. Nevertheless, there are arguments that this did not affect our findings. First, the duration of treatment with phenelzine in our study (6 weeks) is at the upper limit of the 3 to 6 weeks in the other trials with phenelzine in the elderly. Moreover, our follow-up data do not support the suggestion that phenelzine patients may need longer treatment than 6 weeks, as only 2 patients had an advantage of continuation of their MAOI contrary to 5 lithium patients remitting during continuation of the lithium.

Third, there were more psychotic patients in the phenelzine group than in the lithium group (78.6% and 46.7%, respectively), although not being statistically significant in this small group of patients. The 5 patients achieving remission, however, were equally divided among psychotic (N = 2) and nonpsychotic (N = 3) patients, as were the 8 patients who responded to treatment (4 and 4,

respectively). Moreover, all psychotic patients were treated with the combination of an antidepressant and an antipsychotic, as recommended by most experts according to a consensus guideline.[1]

The low rate of early discontinuation of lithium augmentation or of phenelzine indicates overall good tolerance and is better than we had expected in this patient group. There is conflicting evidence of the elderly being at a greater risk than their younger counterparts for developing cognitive side effects with lithium, even when blood levels are within the accepted therapeutic range.[42–44] Neuropsychological testing before and after lithium treatment showed no differences in our sample. Although it is possible that neurotoxic effects of lithium in some patients were counterbalanced by improvement in cognitive functioning as a result of depression improvement in the responding patients. This theory is supported by the only other prospective trial in the elderly presenting data on cognitive function, in which MMSE scores improved during lithium therapy.[21]

Phenelzine was also better tolerated than we expected, as in our trial, no patient had to stop as a result of side effects, compared with 12 of 79 elderly patients (15.2%) dropping out in the 5 uncontrolled trials in the elderly.[16,22–25] A possible difference in tolerance may, however, be masked by starting or increasing the dose of psychiatric comedication, which occurred significantly more often in phenelzine-treated patients than in lithium-treated patients. Monoamine oxidase inhibitors have been reported to be tolerated remarkably well in the elderly, even in a 1-year maintenance study with phenelzine.[43,45] Some studies even found fewer side effects with MAOIs than with TCAs.[23] Most authors conclude that these drugs can be used safely in the elderly when dietary restrictions are observed, which is confirmed by our study.

There are several limitations in our study design. Treatment was not administered in a double-blind manner, although efficacy assessments were performed by a blind interviewer. The number of subjects included in the trial was rather small and may have restricted the power of some analyses. In the uncontrolled trials with elderly patients, however, the mean number of patients receiving lithium augmentation or phenelzine was 16, and the mean number of adult patients randomly assigned to lithium augmentation was 13, which are comparable with our small group sizes.[5] There was no placebo control, as we considered this unethical in patients with severe, treatment-resistant depression, but this means that the proportion of responses due solely to the effect of either medication remains unclear. Although compared with the usually higher exclusion rate in many other RCTs, the exclusion of 51 of 80 eligible patients still may limit the generalizability of our results.

Notwithstanding these methodological limitations, the greater efficacy of lithium compared with phenelzine in our study, as well as the good tolerance of lithium (as with phenelzine), strongly suggests that lithium augmentation deserves a place in the treatment algorithm of elderly patients with major depressive disorder: in the second step as 1 of the options after an antidepressant has failed. As the low efficacy of phenelzine may be explained by its low dose, studies with higher doses are still warranted.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), nortriptyline (Pamelor and others), phenelzine (Nardil), risperidone (Risperdal), selegiline (EMSAM and others), temazepam (Restoril and others), tranylcypromine (Parnate), venlafaxine (Effexor).

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