Outcome of a 4-Step Treatment Algorithm for Depressed Inpatients

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Objective: The aim of this study was to examine the efficacy and the feasibility of a 4-step treatment algorithm for inpatients with major depressive disorder.

Method: Depressed inpatients, meeting DSM-IV criteria for major depressive disorder, were enrolled in the algorithm that consisted of sequential treatment steps (washout period, antidepressant monotherapy, lithium addition, treatment with a nonselective monoamine oxidase inhibitor, electroconvulsive therapy). Definition of nonresponse and progression through the steps of the algorithm was dependent on the score on the 17-item Hamilton Rating Scale for Depression (HAM-D) at predefined evaluation times. Patients were admitted from April 1997 through July 2001.

Results: Of the 203 patients studied, 149 were treated according to the full algorithm, and 54 patients were immediately entered into step 3. Of the 203 patients, 165 (81%) achieved response (≥ 50% reduction in HAM-D score) and 101 (50%) remitted (final HAM-D score ≤ 7). Of the 149 patients treated according to the full algorithm, 129 (87%) responded and 89 (60%) remitted. Twenty-four patients (16%) dropped out from the algorithm.

Conclusion: Although response with antidepressant monotherapy was less than 50%, successive treatment according to the 4-step algorithm was very effective in a sample of depressed inpatients. The adherence to the algorithm was good as shown by a low dropout rate. This study emphasizes the importance of persisting with standardized antidepressant treatment in patients who are initially nonresponders to the first antidepressant. By the end of the study, more than 80% of the patients responded and 50% achieved full remission.

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Although major depressive disorder is considered to have a favorable prognosis, remission rates in controlled studies are considerably less than 50%.[1,2] In recent years, the number of patients who do not respond favorably to antidepressants has increased.[3] Insufficient response to antidepressant treatment is often caused by inadequately performed pharmacotherapy,[4] i.e., inadequate dosage or a suboptimal period of treatment with antidepressants. Since substantial residual symptomatology carries high risk of relapse during continuation treatment and chronic course of the illness,[5] the aim of treatment should be symptomatic remission and functional recovery. Therefore, both inadequate treatment and actual treatment resistance constitute major problems in the management of patients with depression. Applying a systematic treatment algorithm may decrease the variance and increase the appropriateness of antidepressant treatment and, therefore, improve outcome.[4,6]

Based on their review of the efficacy of various biological treatments, Nolen and Haffmans[7] proposed a 4-step treatment strategy in major depressive disorder. It was introduced for clinical practice in the Dutch consensus guideline for the treatment of major depression (CBO).[8]

We have applied this treatment strategy, with a modified second step (lithium addition instead of switching to a second antidepressant). The present algorithm is a rather arbitrary choice out of many possible treatment strategies, i.e., we have selected treatment steps that have shown efficacy in refractory depression. The algorithm has much in common with the Standardized Stepwise Drug Treatment Regimen (SSTR) Algorithm which has

been studied in Germany.[4] The Texas Medication Algorithm Project[9] and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[10] are examples of rather different strategies. The present report focuses on achieving both response and remission during a 4-step treatment, as well as the feasibility of the algorithm. Each of the first 3 steps consists of a double-blind study; the results of these studies are presented elsewhere.[11–13]

METHOD

The study was performed during a 4-year period at the inpatient depression unit of 2 centers: the Department of Psychiatry at Erasmus Medical Centre, Rotterdam (W.W.vdB., J.A.B.) and Parnassia Psychomedical Center, The Hague (T.K.B.), The Netherlands. Both units have a supraregional function for the treatment of treatment-resistant depressed patients (comprising a total of 44 beds for inpatient treatment). It is routine practice to discontinue psychotropic drugs after admission. Depressed patients were screened for inclusion and exclusion criteria. The study protocols were approved by the medical ethics boards of the 2 centers where the study took place, and the studies were performed in accordance with the ethical standards laid down in the World Medical Association Declaration of Helsinki. Eligible patients provided written informed consent after study procedures were fully explained.

Patient Selection

Eligible for inclusion were patients aged 18 to 65 years who fulfilled the DSM-IV criteria for major depressive disorder, which was diagnosed by administration of the depression part of the Schedule for Affective Disorders and Schizophrenia,[14] and who had a Hamilton Rating Scale for Depression (HAM-D)[15] score ≥ 17. Subject exclusion criteria were schizophrenia, schizoaffective disorder, bipolar disorder, organic brain syndrome, chronic alcohol or drug abuse, relevant somatic illness, lack of response to previous adequate treatment with a tricyclic antidepressant (TCA) or fluvoxamine during the index episode, and pregnancy or inadequate contraception for women in the fertile age group. Eligible patients had to be drug free for at least 3 days before study entry. After a 4-day single-blind placebo run-in period, the 17-item HAM-D was administered again. Patients who still met the inclusion criteria of a HAM-D score ≥ 17 and a reduction in HAM-D score < 50% started treatment with either imipramine or fluvoxamine. Patients were admitted from April 1997 through July 2001.

Study Design

The included patients participated in a sequential treatment strategy, consisting of 4 steps:

Step 0: Washout and placebo run-in (1 week)
Step 1: Antidepressant monotherapy (imipramine or fluvoxamine; 6 weeks)
Step 2: Lithium addition (5 weeks)
Step 3: Nonselective monoamine oxidase inhibitor (MAOI; phenelzine or tranylcypromine; 5 weeks)
Step 4: Electroconvulsive therapy (flexible number of weeks)

Antidepressant monotherapy. Patients participating in this double-blind, randomized study received 75 mg of either imipramine or fluvoxamine during days 1 and 2 and then 150 mg during days 3 through 8. Plasma levels of both antidepressants were monitored weekly, and doses were adjusted to attain plasma levels of 200 to 300 ng/mL for imipramine plus desmethylimipramine and 150 to 200 ng/mL for fluvoxamine. Scoring of the 17-item HAM-D and the Clinical Global Impressions (CGI)[16] Severity of Illness and Improvement scales were performed weekly. Less than 10% of the patients received either 1 to 3 mg of lorazepam for excessive anxiety or 1 to 5 mg of haloperidol for intolerable psychotic symptoms. Evaluation of response and remission was done 4 weeks after achievement of an adequate plasma level of the antidepressant.

Lithium addition. For patients with a final HAM-D score > 13 at the end of step 1, lithium was added to the antidepressant (imipramine or fluvoxamine). The initial lithium dose was 600 mg daily. Blood lithium level was measured on day 7 and weekly thereafter, 12 hours postdose. The lithium dose was adjusted to achieve a lithium level of 0.6 to 1.0 mmol/L. Weekly assessment with the 17-item HAM-D and the CGI was performed, and the final evaluation took place 3 weeks after the attainment of the target lithium level.

Nonselective monoamine oxidase inhibitor. For patients with a final HAM-D score > 13 at the end of step 2, both the antidepressant and lithium were discontinued. After a washout period of at least 1 week, treatment was started with either tranylcypromine or phenelzine, at a daily dose of 20 mg. Two times weekly the daily dose could be increased to 40, 60, 80, and 100 mg, respectively, in case of insufficient response (i.e., HAM-D score reduction < 50%). Weekly assessment with the 17-item HAM-D and the CGI was performed; the final evaluation took place after 5 weeks of MAOI treatment. The use of concurrent medication was prohibited, with the exception of lorazepam (maximum dose 3 mg daily). All patients were kept on a tyramine-restricted diet.

Patients with antidepressant-refractory depression at the beginning of the study could be immediately enrolled in step 3 (treatment with a nonselective MAO inhibitor). These patients had received previous treatment with a TCA with therapeutic plasma levels during the index

Table 1. Reasons for Exclusion From a 4-Step Treatment Algorithm for Depressed Inpatients

Exclusion Criterion	N
Resistance to previous adequate antidepressant treatment	56
Bipolar disorder	34
Indication for immediate electroconvulsive therapy	10
Relevant somatic illness	9
Language barrier	5
Total	114

episode. Plasma levels results were sent to and assessed by T.K.B., W.W.vdB., and J.A.B. Patients who had achieved stable plasma levels ≥ 200 ng/mL for imipramine + desmethylimipramine, ≥ 100 ng/mL for amitriptyline + nortriptyline, ≥ 150 ng/mL for clomipramine + desmethylclomipramine, or 50 to 150 ng/mL for nortriptyline during 4 weeks could be included in step 3.

Electroconvulsive therapy. In case of nonresponse to MAOI treatment (HAM-D score > 13 and < 50% reduction in HAM-D score) at the end of step 3, the MAOI was discontinued and, after a 10-day washout, a course of electroconvulsive therapy (ECT) was started. ECT was administered with a brief pulse, constant current apparatus (Thymatron DGx, Somatics Inc, Lake Bluff, Ill.,). Seizure threshold was determined during the first session with stimulus titration. For right unilateral ECT, the dosage exceeded the initial seizure threshold by at least 250%; and for bilateral treatment, by 50%. During the course of ECT, stimulus dosage settings were adjusted upward in order to maintain seizure duration of at least 25 seconds as measured with the cuff method. Patients were treated twice weekly, and clinical evaluation was performed each week using the 17-item HAM-D and the CGI. Patients were initially treated with right unilateral ECT; patients were crossed over to bilateral ECT if response was insufficient after 6 treatments. Patients in a critical condition started with bilateral ECT.

Analysis

We assessed the suitability of the 4-step algorithm by calculating the percentage of patients with major depressive disorder that were actually included in the algorithm. The feasibility is reflected by the number of dropouts, both during treatment and between treatment steps. Finally, we calculated the overall response (reduction in HAM-D score ≥ 50%) and remission (HAM-D final score ≤ 7) to the algorithm on an intent-to-treat basis; for patients who dropped out, the HAM-D score of the last week with treatment is carried forward.

RESULTS

A total of 298 patients with major depressive disorder were admitted to the depression units during the 4-year study period. Of these, 34 (11%) met the criteria for bipolar disorder and were therefore excluded. Of the 264 patients with unipolar major depressive disorder, 80 (30%) fulfilled other exclusion criteria (Table 1). The remaining 184 eligible patients were asked for informed consent, which was refused by 35 patients (19%). Subsequently, 149 patients (50%) were included in the 4-step algorithm. Of the 56 patients who were excluded from step 1 because of proven refractoriness to antidepressants during the index episode, 54 were enrolled directly into step 3 of the algorithm. Only 4 (7%) of these 54 patients had received lithium addition. Ten patients needed immediate ECT. Table 2 presents characteristics of the study population.

Table 2. Characteristics of the Study Population

Characteristic	Patients Entering Study at Step 1 (N = 149)	Patients Entering Study at Step 3 (N = 54)
Age, mean ± SD (range), y	52 ± 9.5 (19–65)	54.2 ± 9.2 (33–65)
Sex, male/female, N	48/101	19/35
Duration of index episode, N (%)		
< 1 year	88 (59)	19 (35)
> 1 year	61 (41)	35 (65)
First episode, N (%)	76 (51)	18 (33)
Psychotic features, N (%)	52 (35)	14 (26)
Adequate pretreatment with antidepressants, N (%)	65 (44)	54 (100)
Baseline HAM-D score, mean ± SD	24.6 ± 5.1	27.3 ± 4.9
Married, N (%)	94 (63)	33 (61)
Education less than high school, N (%)	23 (15)	11 (20)
Living alone, N (%)	43 (29)	19 (35)

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Algorithm

Step 0. Of 149 patients, 11 (7%) responded during a washout and placebo run-in period of 1 week, while 3 (2%) of those achieved remission.

Step 1. Of 138 patients who participated in step 1 (monotherapy with imipramine or fluvoxamine), 57 (41%) were responders. Complete remission was achieved by 32 (23%) of the patients. Seven patients (5%) discontinued antidepressant monotherapy; the reasons for dropout are given in Table 3. Of the 131 patients who completed step 1, 78 (60%) met the criteria for inclusion in step 2 (lithium addition); of those, 6 fulfilled the criteria for response at the end of step 1 and were included in step 2 since they had a HAM-D score of 14 or over.

Step 2. Seven patients who met the entry criteria for step 2 did not receive lithium addition. The reasons for discontinuation between step 1 and 2 are given in Table 3. Of 71 patients participating in step 2 (lithium addition), 42 patients (59%) met the criteria for both response and remission. Seven patients (10%) dropped out during step 2; the reasons for discontinuation are given in Table 3.

Table 3. Reasons for Dropout During the Consecutive Steps of the Algorithm

Reason for Dropout	Step 1: Antidepressant	Between Steps 1 and 2	Step 2: Lithium Addition	Step 3: MAOI	Patients Entering Study at Step 3
Side effects, N	4	0	1	0	1
Worsening, N	2	3	1	0	4
Refused cooperation, N	1	4	3	1	1
Hypomania, N	0	0	1	1	1
Other, N	0	0	1	0	0
Total	7	7	7	2	7

Abbreviation: MAOI = monoamine oxidase inhibitor.

Table 4. Rates of Response and Remission for Each Step and the Overall Algorithm (N = 149)

Step	Total, N	Response, N (%)	Remission, N (%)
Washout	149	11 (7)	3 (2)
Antidepressant monotherapy	138	57 (41)	32 (23)
Lithium addition	71	42 (59)	42 (59)
MAOI	22	10 (45)	5 (23)
ECT	11	9 (82)	7 (64)
Overall algorithm	149	129 (87)	89 (60)

Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor.

Step 3. Of 64 patients completing step 2, 22 (34%) did not achieve remission. All 22 patients fulfilled the entry criteria for step 3 (treatment with a nonselective MAOI: tranylcypromine or phenelzine) and all participated. Two patients (9%) discontinued during MAOI treatment. Ten patients (45%) achieved response, and 5 (23%) met the criterion for remission.

Of the 56 patients who had not responded to adequate treatment with antidepressants prior to admission to the depression unit, 54 (96%) did participate in step 3. Treatment with a nonselective MAOI resulted in response in 25 (46%) of these 54 patients, while 7 (13%) met the criterion for remission. Seven patients (13%) discontinued during MAOI treatment, 1 due to hypomania.

Step 4. At the end of step 3, 12 nonresponders remained. Eleven received ECT; 1 patient (9%) dropped out during the ECT course. Eight patients received bilateral ECT and 3 were treated with right unilateral ECT. The mean number of treatments was 12.5. Nine patients (82%) responded to ECT and 7 (64%) achieved remission.

With regard to the 22 patients who entered at step 3 of the algorithm and did not respond to treatment with a nonselective MAOI, 13 (62%) of them received ECT, which resulted in response in 11 patients (85%). Five (38%) of the 13 patients achieved remission with ECT. A summary of efficacy data is given in Table 4.

Overall Result of the Algorithm

At the end of the algorithm, 129 (87%) of 149 patients achieved response. Complete remission was achieved by 89 of 149 (60%) patients. Three patients switched into hypomania during the algorithm: 2 receiving a combination of imipramine and lithium and 1 patient receiving phenelzine. These patients were considered both as responders and remitters. Overall dropout of the algorithm amounted to 24 (16%) of 149 patients. When including patients who entered the algorithm at step 3 (treatment with a nonselective MAOI) the figures are as follows: 165 (81%) of 203 responded during the algorithm and 101 (50%) achieved remission. Overall dropout, including the 54 additional patients, was 30 of 203, i.e., 15%.

DISCUSSION

Of all the patients admitted to the depression units with a major depressive disorder, 50% participated in the 4-step algorithm. The most frequent reason for nonenrollment in phase 1 was proven refractoriness to previous adequate treatment with either a tricyclic antidepressant or fluvoxamine during the index episode. With respect to patients who previously received adequate treatment with antidepressants, almost all of them (54 of 56) were enrolled in step 3 of the algorithm; if these latter patients are considered participants, since they entered the algorithm at step 3, the percentage of participating patients rises to 68%.

Almost 20% of the eligible patients refused to provide informed consent, even though the staffs of both units were very experienced in informing patients about study procedures.

The patients who did participate suffered from severe major depressive disorder, which can be concluded from both the mean baseline 17-item HAM-D score (24.6) and the proportion of patients with psychotic depression (35%). A relatively large percentage of patients (41%) had an index episode lasting over 1 year. For the participating patients, the 4-step algorithm appeared to be very effective, as shown by a favorable outcome in terms of both response (87%) and remission (60%). Cuffel et al.[17] reported only 30% remission in their clinical practice. The response rate in the present study is in fact very close to 96% hypothetical cumulative response rate to a series of antidepressants and ECT, predicted by Thase and Rush.[18]

Our results demonstrate the importance of persisting with alternative antidepressant treatment when patients

show nonresponse to the first antidepressant. There are several explanations for why our results are more favorable than expected. The higher remission rate in the present study may be due to the specialized character of both depression units. Both units are almost exclusively reserved for patients with severe depression. The first unit (Erasmus Medical Centre) has a large staff, including 2 psychiatrists, 2 residents, nurses, and a social worker, as well as an activation and a psychomotor therapist. The staff of the second unit (Parnassia) consists of 1 psychiatrist, 1 resident, and the disciplines mentioned above. Patients participate in a rather intensive treatment program including group (cognitive and psychoeducation) psychotherapy.

Since both careful monitoring and the participation in a structured treatment program probably contributed to the encouraging results of the algorithm, the outcome of a similar algorithm for depressed outpatients may be less favorable.

Furthermore, refraining from prescribing benzodiazepines and antipsychotics as concomitant medication may have contributed to the efficacy of the algorithm. In clinical practice, many depressed patients receive concomitant psychotropic medication, even though this might actually decrease the efficacy of antidepressants. The literature is inconclusive about a possible diminished efficacy with a benzodiazepine-antidepressant combination, but the results of 2 studies hint at a negative effect of benzodiazepines.[19,20] The overall response rate and remission rate during step 1, antidepressant monotherapy, were relatively modest, 41% and 23%, respectively. This may be due to the inclusion of many patients who had been pretreated with antidepressants and/or whose major depressive episode lasted over 1 year. Although the response to antidepressant monotherapy was modest, plasma-level targeted dosing may have enhanced the efficacy of both antidepressant monotherapy[21] and lithium addition. Patients were closely supervised by the nursing staff, probably resulting in good treatment compliance.

Step 2, lithium addition, was remarkably successful, as shown by a 59% remission rate. About 30% of the patients responded to lithium addition within the first week.

The overall response to nonselective MAOIs (45%) can be considered a satisfactory result in patients with severe treatment-resistant depression. This response rate is virtually the same for patients entering the algorithm at step 3, even though patients following the algorithm had been pretreated with lithium addition, whereas patients starting at step 3 had not. The remission rate was relatively low for both samples (23% versus 13%). Although the discontinuation during phase 3 was fairly low (12%), orthostatic hypotension was a dose-limiting factor in some patients. Regarding step 3, aiming at high MAOI doses (mean doses: 60 mg for tranylcypromine and 79 mg for phenelzine) may well have contributed[22] to their efficacy in these treatment-resistant patients.

Patients failing 3 consecutive antidepressant treatments still showed a favorable response to ECT and the majority (64%) achieved remission at the end of the ECT course. In the present study, medication resistance barely affected response to ECT, which is in accordance with previous Dutch studies.[23,24]

The fact that all treatment steps implemented in this algorithm are established, "old" treatments may also account for its favorable outcome. Algorithms consisting of newer antidepressant treatments or new combinations preferably should be compared with an established algorithm.

In the study by Adli et al.[4] a favorable outcome based on a similar stepwise treatment algorithm was also found. Both algorithms have much in common, since both include subsequent treatment with antidepressant monotherapy, lithium addition, a nonselective MAOI and ECT. The authors attributed their good outcome to the adherence to the algorithm per se, which implies a structured treatment course with few treatment switches and a longer study period of their algorithm as compared to most antidepressant trials. It is difficult to compare our results with those of Adli et al.[4] because they used scores on the Bech Rafaelsen Melancholia Scale[25] as outcome criteria; both their response rate (72%) and remission rate (38%) are lower than attained with our algorithm.

The Texas Medication Algorithm Project[9] is very different from ours; because it has 7 treatment steps with considerable variation within the specific steps, a comparison between our results and theirs is not feasible. Moreover, their study only presents the difference in the reduction of the 30-item Inventory of Depressive Symptomatology (Clinician Rated) score between the algorithm and treatment as usual, without stating the number of patients in remission. The STAR*D project[10] is a multisite randomized trial for depressed outpatients consisting of 4 treatment steps for nonresponders to citalopram; again, because of the variation within treatment steps, a comparison with our algorithm is not feasible. Flint and Rifat[26] evaluated the efficacy of an antidepressant treatment algorithm in elderly depressed patients. Their algorithm bears some similarity with ours, but they employed 3 additional treatment steps; their results are excellent, since 83% of the patients attained a final HAM-D score of 10 or less. Quitkin et al.[27] also achieved a very good remission rate (66%) as a result of 3 consecutive antidepressant trials in a sample of 591 depressed outpatients.

The main limitation of the present study is the lack of a control group receiving "treatment as usual," and the lack of blind ratings.

In conclusion, our results strongly emphasize the importance of persisting with stepwise antidepressant treatment in nonresponders to the first antidepressant. Our algorithm appeared to be very effective in inpatients referred to depression units specialized in the treatment of refractory depression; these patients have been character-

ized as having an unfavorable treatment response.[28] Adherence to the algorithm was good, as shown by an overall dropout rate of 15%.

Drug names: citalopram (Celexa, and others), clomipramine (Anafranil and others), imipramine (Tofranil), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), nortriptyline (Pamelor, Aventyl, and others), phenelzine (Nardil), tranylcypromine (Parnate).

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