Effectiveness and Feasibility of a Standardized Stepwise Drug Treatment Regimen Algorithm for Inpatients With Depressive Disorders: Results of a 2-Year Observational Algorithm Study

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Background: The goal of the Berlin Algorithm Project is to establish a standardized stepwise drug treatment regimen (SSTR) for the treatment of inpatients with depressive disorders. We are reporting on the first of 3 subsequent study phases evaluating effectiveness and feasibility of the SSTR in a naturalistic clinical setting.

Method: Patients with depressive disorders (*International Classification of Diseases,* Ninth Revision criteria) admitted to an academic medical center for inpatient treatment were enrolled in the SSTR protocol that comprised an algorithm-guided sequential treatment process (including pharmacologic washout period, sleep deprivation, antidepressant monotherapy, lithium augmentation, monoamine oxidase inhibitor treatment, and electroconvulsive therapy) dependent on the scores of a standardized assessment of treatment outcome, the Bech Rafaelsen Melancholia Scale (BRMS).

Results: Of 248 patients with depression, 119 (48%) were enrolled in the SSTR protocol. One hundred twenty-nine patients (52%) were not included, mostly due to individualized treatment procedures. An intent-to-treat (ITT) analysis showed that 38% of enrolled patients achieved remission (BRMS score ≤ 5), 34% achieved "classic" response (ΔBRMS score ≥ 50%), 15% achieved "low" response (ΔBRMS score 26% to 49%), and 13% did not respond. The overall response rate (remitters and classic responders) of SSTR treatment was 72% of the ITT sample. Twenty-one patients (18%) dropped out from the SSTR as nonresponders and 19 patients (16%) dropped out as low responders due to protocol deviations.

Conclusion: The acceptance of the antidepressive treatment algorithm among physicians not specifically trained was moderate, resulting in a relatively low enrollment rate. However, once patients were enrolled into the study, adherence to the algorithm-based rules resulted in a low dropout rate. Most importantly, algorithm-guided antidepressive treatment showed a favorable response in those depressed patients who were treated according to the SSTR protocol.

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In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Aldi, Berghöfer, Linden, Helmchen, Müller-Oerlinghausen, Machert, and Bauer and Mr. Stamm have no significant commercial relationships to disclose relative to the presentation.

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In spite of dramatic increases in the number of antidepressants, drug combinations, and augmentation strategies available over the past 20 years, treatment-resistant depressive disorders remain a significant problem in clinical practice.[1–7] In recent years, psychiatrists in practice, academic referral centers, and research settings increasingly observe patients with depressive disorders who are inadequately responsive to drugs used in monotherapy or in combinations.[8] As many as 30% to 40% of patients with depressive disorders do not respond to the first course of drug treatment chosen, and another 50% of those nonresponders do not respond to a second, different course of treatment. A residual group of patients does not achieve adequate relief from depression and develops a chronic course of the illness.[3,9] Given the high 1-year prevalence rate of about 10% in the general population[10] and considering the socioeconomic consequences of these conditions,[11,12] it is evident that the development of novel strategies and systematic approaches for the treatment of patients with depressive disorders deserves special attention.

Inadequately performed pharmacotherapy and unsystematic treatment plans have been suggested to be major contributors to an unfavorable treatment outcome.[1] In

clinical practice, treatment resistance frequently results from inadequate dosage and an inappropriate length of treatment with antidepressants or from insufficient use of the available therapeutic repertoire in the case of incomplete response. Some studies indicate that only a minority of treatment-resistant patients are "absolute" resistors and that the majority of "relative" resistors (who have failed to respond to a minimally adequate treatment without application of strategies recommended for nonresponders) can be helped substantially by rigorous treatment approaches including a course of electroconvulsive therapy (ECT).[9] Also, some evidence suggests that repeated drug trials, per se, may be associated with treatment-resistant depression.[13] Specifically, data have indicated that the probability of responding to an antidepressant declines by a factor of approximately 15% to 20% for each failed drug treatment.[14] The assumption behind the development of systematic treatment algorithms is that decreasing the variance and increasing the appropriateness of treatment strategies results in enhanced patient outcomes and the avoidance of refractoriness.[13,15–18] It has been suggested that algorithms may provide an effective means to optimize outcomes in clinical benefits and cost effectiveness.[1,15]

A standardized stepwise drug treatment regimen (SSTR) is one example of such a systematic treatment approach. SSTRs are empirically derived protocols based on sequential application of a variety of single therapeutic steps.[17] We have used an SSTR as a systematic treatment algorithm for inpatients with depressive disorders.[1,2,17] To evaluate the feasibility, effectiveness (therapeutic effect of a certain intervention in view of a defined therapeutic goal), and efficacy (therapeutic effect of a certain intervention proven in a controlled clinical trial) of the SSTR in clinical practice, we initiated a multistep project (the Berlin Algorithm Project) consisting of 3 major phases: phase 1 was an observational 2-year pilot study to evaluate the effectiveness, feasibility, and acceptance among the algorithm users; phase 2 was a randomized, controlled, single-center study to evaluate treatment efficacy and treatment process compared with standard treatment as usual; and phase 3 was a nationwide, randomized, controlled study to evaluate treatment efficacy and efficiency compared with standard treatment as usual (within the Research Network on Depression supported by the German Ministry for Education and Research). Preliminary results of the first year of the pilot study (phase 1) were published earlier[17,19]; here we report the final results of the 2-year pilot study.

METHOD

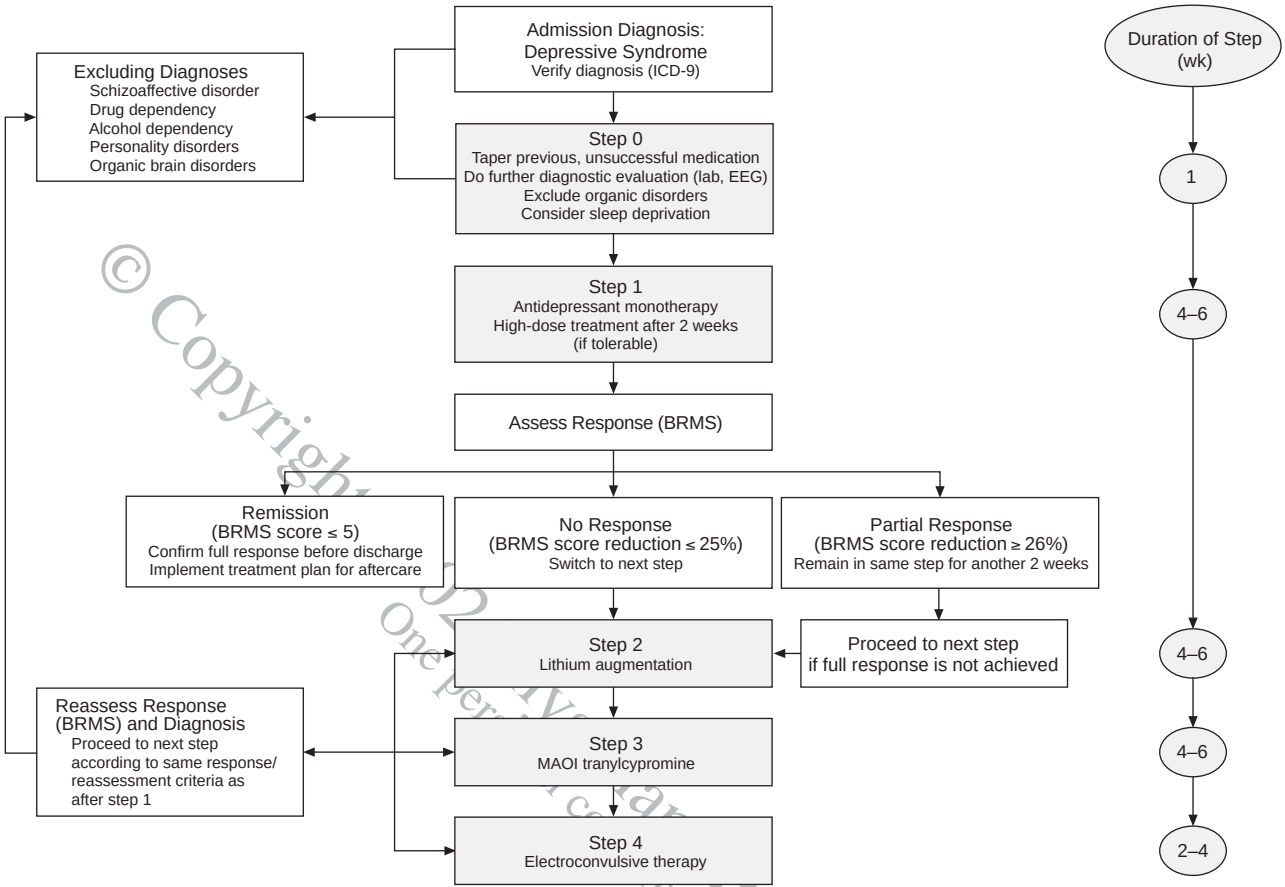
The SSTR was developed by a consensus group of senior psychiatrists at the Department of Psychiatry, Freie Universität Berlin, Berlin, Germany. The final version, introduced into the clinical setting in 1990, reflected the reviewed literature at that time as well as individual clinical experiences of the consensus group members. The Berlin Algorithm Project strived to make the SSTR as free of bias as possible toward any drug or drug class and was supported not by external funding but by departmental resources only. It also intended to represent a synthesis of current scientific knowledge on the treatment of depressive disorders. In a first prospective pilot study conducted between 1990 and 1992, acceptance and effectiveness of the SSTR was tested in a naturalistic clinical setting. Effectiveness was determined by standardized assessment of clinical outcome with the Bech Rafaelsen Melancholia Scale (BRMS).[20] Acceptance was indirectly assessed by evaluating rates of inclusion and exclusion by the treating physicians and documentation of the reasons for exclusion.

All patients admitted to the 6 wards (comprising a total of 108 beds for inpatient treatment) of the Freie Universität Berlin Department of Psychiatry (academic medical center) over a 2-year period with the diagnosis of "depressive syndrome" were screened for inclusion and exclusion criteria by clinical interview. Patients with the following diagnoses according to the *International Classification of Diseases,* Ninth Revision (ICD-9),[21] were subsequently included in the SSTR protocol (Figure 1) (ICD-9 codes given in parentheses): endogenous depression (296.1), reactive depressive psychosis (298.0), bipolar affective disorder, depressed (296.3), and neurotic depression (300.4). Patients fulfilling the following diagnoses or criteria were excluded from the SSTR protocol: (1) schizoaffective disorder, (2) substance dependency, (3) personality disorder, (4) ongoing prophylactic medication with a mood stabilizer, e.g., lithium or carbamazepine, and (5) a specific indication for a different treatment approach other than intended in the SSTR protocol, e.g., history of a successful treatment response to a particular antidepressant or urgent clinical requirement of ECT.

Characteristics and Structure of the SSTR

The primary feature of the SSTR algorithm is a stepwise medication change based on the results of clinical evaluation with the BRMS at 2-week intervals (Figure 1). The BRMS is an established clinical rating scale consisting of 11 items, each rated from 0 to 4. Validity studies have yielded high positive correlations ($r = 0.86$) between the BRMS and the Hamilton Rating Scale for Depression.[22,23] The SSTR algorithm defines *no response* to treatment as a reduction in the BRMS score by 25% or less within a treatment step, *partial response* as a reduction by 26% or more, and *remission* as a BRMS score of 5 or less. For outcome evaluation only, we divided patients with partial response into 2 groups: patients with a BRMS score reduction of ≥ 50% without achieving remission ("classic" responders) and a BRMS score reduction between 26% and 49% ("low" responders). By dividing partial responders into 2 groups, the effectiveness of the

Figure 1. Standardized Stepwise Drug Treatment Regimen (SSTR) Procedures in Inpatients With Depressive Disorders[a]



[a]Abbreviations: BRMS = Bech Rafaelsen Melancholia Scale; EEG = electroencephalogram; ICD-9 = *International Classification of Diseases,* Ninth Revision; lab = routine laboratory blood assessment; MAOI = monoamine oxidase inhibitor.

treatment steps can be evaluated both by the criterion of response (ΔBRMS score ≥ 50%), which is used in most clinical trials, and by the criterion of remission (BRMS score ≤ 5). The BRMS score reduction is based on each previous rating taken at the beginning of a particular step. In cases of nonresponse after completion of the current step, patients begin the next step. Partial responders do not switch to the next step but instead remain in the current step for another 2 weeks. This is only allowed once per step. In cases of persistent partial response at the next critical decision point, a switch to the next treatment step is mandatory. Remitted patients remain at the current step until discharged. For the purpose of this study, ratings were performed by a nonblinded ward psychiatrist or resident in psychiatry at the end of each step between 10 a.m. and noon. All raters completed a video training on how to use the BRMS. An interrater reliability test yielded a high intraclass correlation coefficient (ICC = 0.87).[24]

The SSTR consisted of up to 5 sequential treatment steps (step 0 to step 4) (Figure 1). The goals of step 0 during the first week of admission were to taper previous (unsuccessful) medication and observe spontaneous remission after admission to the hospital, perform diagnostic evaluations and assess severity of depression before the onset of new medication. During step 0, one or two courses of total or partial sleep deprivation could be performed to improve depressive symptoms. After this 1-week discontinuation period, the initial response (improvement due to nonspecific effects of admission and sleep deprivation) was assessed before entry into step 1. Step 1 was 4 weeks of antidepressant monotherapy with a tricyclic antidepressant (TCA) amitriptyline, nortriptyline, or clomipramine (the choice of drug was not determined by protocol). The TCA was administered at a dose of 150 mg/day in the first 2 weeks (step 1) followed by another response assessment. In case of no response, increasing the dose to 300 mg/day for another 2 weeks was suggested, if tolerated by the patient.

The following steps included augmentation with lithium (at blood lithium levels of 0.5–1.0 mmol/L) for 4 weeks (step 2), discontinuation of all psychotropic medication for 1 week and subsequent treatment with the

Table 1. Timepoint and Reasons for Dropout From the Standardized Stepwise Drug Treatment Regimen Protocol (N = 119)[a]

	Timepoint of Dropout							
	Step 0		Step 1		Step 2		Step 3	
Reasons for Dropout	NR	LR	NR	LR	NR	LR	NR	LR
Change of therapeutic regimen								
Related to psychiatric diagnosis	2[b]	0	4[c,d]	1[e]	0	0	2[f]	0
Due to intolerable side effects	0	0	6	10	1[g]	0	0	0
Premature discharge/ transfer to another hospital	2	0	1	2	3	4	0	2
Total dropouts (N = 40)	4	0	11	13	4	4	2	2

[a]Abbreviations: ECT = electroconvulsive therapy, LR = low response, NR = nonresponse.
[b]Change of diagnosis and suicide attempt in 1 patient.
[c]Change of diagnosis in 2 patients.
[d]Change of antidepressant and ECT in 1 patient each.
[e]Acute suicidality.
[f]Withdrawal of consent, no consent in ECT.
[g]Adverse drug effect and subsequent switch to ECT.

irreversible monoamine oxidase inhibitor (MAOI) tranylcypromine (up to 30 mg/day) for 4 weeks (step 3), and discontinuation of MAOI treatment and preparation for ECT and a subsequent course of ECT for another 2 to 4 weeks (step 4; usually bilateral ECT, 3 sessions/week). During the SSTR procedures, concomitant neuroleptic medication (haloperidol or perazine) was accepted only for depressive disorders with psychotic symptoms. TCA drug monitoring at 2-week intervals during steps 1 and 2 was suggested to exclude toxic TCA plasma levels; subsequent dose adjustments were proposed.

Supportive psychiatric management, including occupational therapy, was continuously provided throughout the entire SSTR protocol, as usual. However, specific individual or group psychotherapy was not considered part of the SSTR protocol.

Overall treatment response to the SSTR was assessed on the basis of improvement in BRMS scores from baseline (after step 0). Premature SSTR protocol exits of nonresponders and low responders were regarded as dropouts whereas SSTR protocol exits of classic responders were not, since a BRMS score reduction of ≥ 50% was accepted as sufficient improvement for the discharge of a patient. The reasons for dropout during the SSTR procedure were categorized into 3 clusters; results for each treatment step are listed in Table 1.

Statistical Analysis

The total study population was analyzed for possible initial (placebo) response during the medication-free period in step 0 caused by nonspecific effects, such as hospital admission. Analysis was done using a 2-tailed t test for paired samples comparing mean BRMS scores at baseline and after step 0. A 2-tailed t test for independent samples was performed to compare BRMS scores before entry into step 1 between remitters to steps 1 and 2. The same procedure was performed for classic responders to both steps. The applied treatment step served as an independent variable. The significance level was set at .05. Differences in baseline BRMS scores between the outcome groups were analyzed by analysis of variance (ANOVA) post hoc Scheffé procedure. All statistical procedures were performed with the SPSS 9.0 package for Windows.[25]

RESULTS

A total of 328 patients prediagnosed with a "depressive syndrome" by the referring physician were admitted to the hospital during the 2-year study period. Of these, 80 patients (24%) were not treated according to the SSTR protocol because of an excluding diagnosis. Of the remaining 248 patients, 129 (52%) were excluded due to particular reasons included in the study's protocol (see Method and Figure 2). Subsequently, 119 patients (48%) were enrolled in the SSTR protocol (this group of patients is labeled "total study population" throughout; for clinical and demographic characteristics see Table 2).

SSTR Protocol

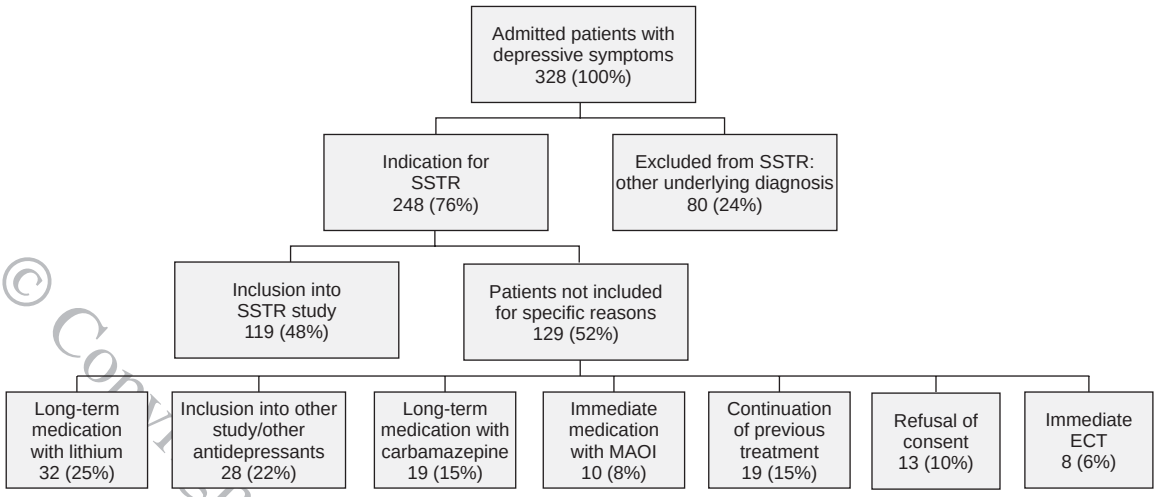
Step 0. Of the total study population, 4 patients dropped out of the SSTR protocol during or after step 0. The mean ± SD BRMS score changed from 20.0 ± 5.9 at study entry to 18.6 ± 5.9 at the end of step 0 ($T = 4.003$; $p < .001$).

Step 1. Of 115 patients who completed step 1 (antidepressant monotherapy), 25 (22%) patients were remitters, 65 (57%) were partial responders (33 [29%] classic responders, 32 [28%] low responders), and 25 (22%) did not respond (nonresponders) (Figure 3).

Not all nonresponders to the initial standard antidepressant dosage during the first 2 weeks of step 1 were administered a higher dose (>150 mg/day) of antidepressant. Eleven of 52 nonresponders to the first 2 weeks of step 1 continued the initial antidepressant dose of 150 mg/day during the entire step 1, 29 patients had the dose of the antidepressant raised to 225 mg/day, and 12 patients had the dose raised to 300 mg/day. Of the initial 68 partial responders, 8 classic responders and 19 low responders at step 1 immediately proceeded to the next step without the suggested prolongation of the current treatment step. Twenty-five classic responders at step 1 were discharged after response was considered to be sufficient. Only 3 low responders stayed in step 1 and achieved remission after prolongation. Eleven of the 25 patients who did not respond and 13 of the 35 low responders dropped out of the protocol for various reasons at step 1 (Table 1).

The mean ± SD BRMS score after step 1 was 3.9 ± 0.9 for remitters, 8.4 ± 1.8 for classic responders, 12.1 ± 3.8 for low responders, and 16.6 ± 6.4 for nonresponders

Figure 2. Overview of the Screening Procedures and Reasons for Exclusion From the SSTR Protocol[a]



[a]Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSTR = standardized stepwise drug treatment regimen.

Table 2. Clinical and Demographic Data of 119 Subjects Enrolled in the Standardized Stepwise Drug Treatment Regimen[a]

Characteristic	Value
Age, mean ± SD, y	51.8 ± 13.3
Gender, N	
Male	39
Female	80
Diagnosis (ICD-9), N	
Endogenous depression, monopolar (296.1)	78
Depression, bipolar (296.3)	10
Neurotic depression (300.4)	7
Reactive depressive psychosis (298.0)	16
Other depressive states, NOS (311.0)	8

[a]Abbreviations: ICD-9 = *International Classification of Diseases*, Ninth Revision; NOS = not otherwise specified.

(Table 3). The mean ± SD BRMS score for the total study group after step 1 was 10.5 ± 5.7. There was a significant difference in BRMS score between remitters and classic responders prior to entering step 1 (mean ± SD intergroup difference 5.7 ± 1.6, $p < .01$). No significant difference was found between the low responders and nonresponder groups after step 1.

Step 2. During the 4-week lithium augmentation step, remission was achieved in 14 (34%) patients (mean ± SD BRMS score = 3.6 ± 1.6), partial response in 15 patients (37%) (6 classic responders, BRMS score = 7.0 ± 1.7; 9 low responders, BRMS score = 7.8 ± 0.97), and nonresponse in 12 patients (29%) (BRMS score = 14.2 ± 5.3) (Figure 3, Table 3). All 6 classic responders were discharged with a response that was regarded as sufficient without the suggested prolongation of the treatment step. Of the 9 low responders, 4 were discharged and another 5 remitted after prolongation of the step (thus, the number of remitted patients in this step increased to 19 [46%]). Four of the nonresponders dropped out, and 8 nonresponders proceeded to step 3. There was no significant difference between the different responder groups after step 2 with regard to baseline BRMS scores (data not shown).

There was no significant difference in baseline mean ± SD BRMS score between remitters in step 1 (15.3 ± 4.2) and step 2 (17.6 ± 4.9) ($T = –1.477$, $p = .15$) or between classic responders to step 1 (20.9 ± 4.7) and step 2 (22.4 ± 6.1) ($T = –0.515$, $p = .63$).

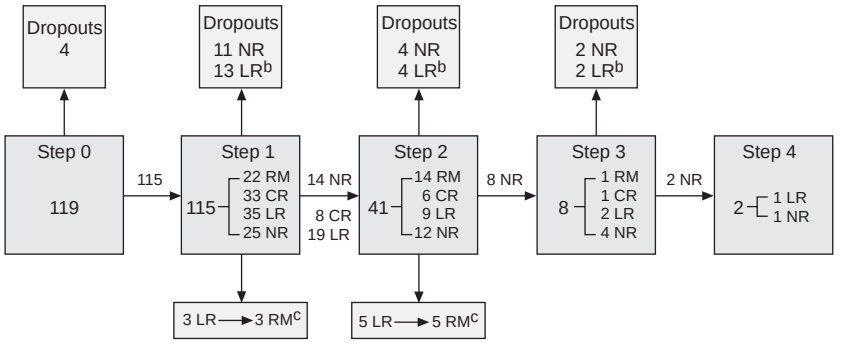
Step 3. Of the 8 nonresponders who proceeded to step 3 (MAOI treatment), 1 achieved remission, 1 was discharged with a classic response, and 2 were discharged with a low response. Of the 4 nonresponders, 2 dropped out of the protocol at the end of this treatment step and 2 proceeded to step 4 (Figure 3).

Step 4. This final step (ECT) led to low response in 1 patient and nonresponse in another. Due to the small subgroups, ANOVA procedure could not be performed to compare baseline BRMS scores for the different response groups in steps 3 and 4.

Overall Response

Of the 119 patients (intent-to-treat [ITT] population) entering the protocol at step 0, 45 patients were remitters (38%), 40 patients (34%) were classic responders, 18 patients (15%) were low responders, and 16 patients (13%) were nonresponders during the study. Of the nonresponders, 1 patient did not achieve response despite adhering to the protocol; the other nonresponders dropped out of the protocol before achieving response. Thus, the overall rate of responders (remitters + classic responders) to SSTR was 72%. Of the study completers (N = 79), 57% achieved remission and 41% achieved classic response (total response rate = 98%). The cumulative response rates to the subsequent treatment steps are shown in

Figure 3. Overview of Attrition, Number of Responders, and Dropouts During the Different Steps of the SSTR Protocol[a]



Cumulative Response	Step 1 Antidepressive Monotherapy, N	Step 2 Lithium Augmentation, N	Step 3 MAOI, N	Step 4 ECT, N
Remission	25	44	45	45
Classic Response	33	31	32	32
Overall Response	58 (49%)	75 (63%)	77 (65%)	77 (65%)

[a]Response categories depend on the Bech Rafaelsen Melancholia Scale (BRMS) score reduction at the end of the previous step. Abbreviations: CR = classic responders, ECT = electroconvulsive therapy, LR = low responders, MAOI = monoamine oxidase inhibitor, NR = nonresponders, RM = remitters (full remission).
[b]Patients with low response who were discharged.
[c]Patients with low response who remained in the same step for another 2 to 3 weeks and remitted during this time.

Table 3. Number of Subjects and Mean BRMS Scores at Study Entry and at the End of Each Step[a]

	Step 1		Step 2		Step 3		Step 4	
Outcome Status	N	BRMS ± SD	N	BRMS ± SD	N	BRMS ± SD	N	BRMS ± SD
Remission	22	3.9 ± 0.9	14	3.6 ± 1.6	1	5.0	…	…
Classic responders (ΔBRMS ≥ 50%)	33	8.4 ± 1.8	6	7.0 ± 1.7	1	8.0	1	7.0
Low responders (ΔBRMS 26%–49%)	35	12.1 ± 3.8	9	7.8 ± 1.0	2	9.5 ± 0.7	…	…
Nonresponders (ΔBRMS ≤ 25%)	25	16.6 ± 6.4	12	14.2 ± 5.3	4	18.2 ± 0.5	1	14.0
Total	115	10.5 ± 5.7	41	8.1 ± 5.2	8	13.1 ± 5.7	2	10.5 ± 4.9

[a]Without prolongation phases; after the 1-week washout/sleep deprivation phase, the mean ± SD BRMS score at the end of step 0 was 18.6.
Abbreviation: BRMS = Bech Rafaelsen Melancholia Scale.

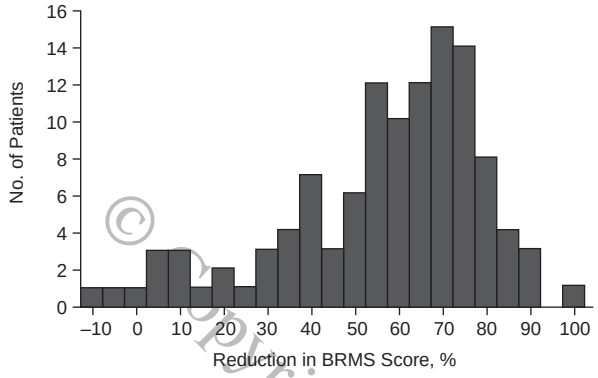
Figure 3. Figure 4 illustrates the overall BRMS score reduction during the SSTR treatment for all patients entering the SSTR in step 1. Overall, 21 patients (18%) dropped out of the SSTR as nonresponders, and 19 patients (16%) dropped out as low responders (premature protocol exits; see Table 1). Thirty-two patients left the protocol after having achieved classic response (ΔBRMS score ≥ 50%). None of the patients switched into mania/hypomania during participation in the SSTR protocol.

DISCUSSION

A relatively large proportion (24%) of patients prediagnosed by the referring physicians with a depressive syndrome did not qualify for the SSTR protocol after hospital admission due to an excluding diagnosis. Of those who fulfilled inclusion criteria, another 52% were not enrolled into the SSTR protocol, largely due to the particular treatment needs of the individual participant. The most frequent reason for nonenrollment was the patient's preexisting medication treatment with a mood stabilizer. Exclusion from the SSTR, for the purpose of individualizing treatment procedures, was most likely due to nonacceptance of the algorithm-guided treatment by some of the treating physicians. Although not evaluated systematically, one of the reasons for physician nonacceptance may have been a disagreement with the specific SSTR procedures during step 1 (patients were either kept on their previous medication or were given other compounds divergent from the protocol, e.g., nontricyclic antidepressants). Also, some depressed patients who were considered already treatment refractory before admission may have been immediately assigned to established strategies for treatment-resistant patients (e.g., ECT). Avoiding inclusion of a patient into a systematic treatment algorithm may have also been due to physicians' concerns regarding algorithm commitment and loss of flexibility in treatment execution.

Of the patients who entered the SSTR, 38% showed full remission (57% of the study completers), 34% showed classic response, and 15% achieved low response. These rates of remission and response are a relatively

Figure 4. Reduction of BRMS Score During SSTR Treatment of the Total Population Entering the SSTR in Step 1 (N = 115)[a]



[a]Mean ± SD percentage of BRMS score reduction = 56.8 ± 22.8.
Abbreviations: BRMS = Bech Rafaelsen Melancholia Scale, SSTR = standardized stepwise drug treatment regimen.

favorable overall outcome for depressed inpatients at a tertiary care academic center. Short-term response rates (usually defined as a symptom reduction of ≥ 50%) in ITT samples of randomized-controlled trials (RCTs) are about 50% to 70% with antidepressants, but only about 30% of patients will experience remission.[3,26–29] The main reason for the favorable outcome in this study may be the fact that the study period was not limited to a certain time frame (e.g., 4–8 weeks), as in most RCTs, but continued until the preset outcome criterion (remission) was achieved. Another reason for the favorable results here may be the exclusion of those patients from the SSTR treatment that had more complicated or treatment-refractory courses of the illness. However, we cannot prove the latter possibility because those patients who were not eligible or who dropped out of the SSTR protocol were not systematically followed up.

We found a relatively high rate of premature study exits in the group of partial responders. Instead of extending the current treatment step and following the protocol until remission, one third of enrolled patients left the protocol after having achieved partial response, and only a few classic responders with a BRMS score reduction of ≥ 50% during a treatment step proceeded to the next step. However, a score reduction of ≥ 50% is regarded as a symptom improvement sufficient to continue treatment on an outpatient basis, which leads to patients' discharge.

There was a significant difference between the baseline BRMS scores of remitters and classic responders to step 1. Patients achieving remission after an initial treatment trial seemed to be less severely depressed than those who only achieved a partial improvement of symptoms, which is in line with previous studies.[30,31] However, patients remitting after initial antidepressive monotherapy could not be differentiated from those remitting after subsequent lithium augmentation based on their initial BRMS score. The worsening of BRMS score from 8.1 after step 2 to 13.1 after step 3 may be explained by a remaining subpopulation of highly refractory and severely depressed patients.

The response rates did not show a considerable increase once the lithium augmentation step was completed. A higher dose of tranylcypromine, which has been shown in open trials to be effective in refractory depressed patients,[32] may have led to a better outcome during step 3. The maximum dose of 30 mg/day of tranylcypromine was chosen because this was the recommended dose at the time of study initiation (*Rote Liste*, the German equivalent to the U.S. *Physicians' Desk Reference*), and orthostatic hypotension, a common side effect of the agent, could be avoided.[32] However, as a consequence of the low response rate in this study, as well as the observed tolerability of the 30-mg/day dosing regimen, the recommended dose of tranylcypromine was later increased in phases 2 and 3 of the Berlin Algorithm Project.

The SSTR presented here is one possible algorithmic strategy in the pharmacotherapeutic armamentarium of depressive disorders. The more selective antidepressants (e.g., selective serotonin reuptake inhibitors) were not available at the time of study initiation. Alternative procedures for the treatment of nonresponders to antidepressive monotherapy would also have been possible (e.g., switching to an antidepressant with a different pharmacodynamic profile or augmenting with a different agent than lithium, e.g., thyroid hormone or buspirone).[29,33] Generally, we chose treatment strategies (lithium augmentation, MAOI, ECT) that have been shown effective in treatment-resistant depression.[29,34–36] We did not consider switching to an antidepressant of a different profile in step 2 because the majority of patients admitted to our tertiary care institution had already been treated with 1 or more antidepressants during their outpatient treatment.[1,2] However, one might argue that the strategy chosen is actually of secondary importance. It may be hypothesized that the most important therapeutic factor is adherence to the algorithm-guided procedure per se, which leads to a highly structured treatment course with few strategy switches and drug combinations, and rational medical decision making following standardized rules.

This study had a few more limitations, which we have tried to overcome in our phase 2 and phase 3 projects.[37] First, patients not entering the SSTR protocol, as well as dropout patients, were not systematically monitored after quitting the study. Second, unipolar as well as bipolar depressed patients were included in the study. This reflects treatment tradition in Germany, where antidepressants were used more often in bipolar depressed patients in the early 1990s. However, only patients without an ongoing prophylactic treatment with a mood stabilizer were included. Third, the primary rating scale used was the BRMS, which is not very common in the United States

and makes direct comparisons with other studies of this kind more difficult. Fourth, we did not assess consumption of concurrent psychotropic drugs (e.g., benzodiazepines and neuroleptics), which is assumed to decrease with the introduction of a structured algorithm-guided treatment.

In the past, algorithm-guided and systematic treatment procedures for depressive disorders have rarely been studied systematically.[38,39] The Texas Medication Algorithm Project, a multicenter project in the United States, studies the impact of treatment algorithms for different psychiatric disorders in a prospective matched-study design.[40] From this ongoing project, it was recently reported that outpatients with major depression who were treated according to an algorithm presented a significantly stronger symptom reduction and improvement in mental functioning than matched patients who received treatment as usual.[41] Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a National Institute of Mental Health–funded, multisite clinical trial, is currently underway in the United States. STAR*D evaluates stepwise treatment procedures in depression and particularly addresses an evaluation of different strategies in patients who are not responding to an initial antidepressant trial.[42] The Berlin Algorithm Project, of which phase 1 is presented in this article, intends to investigate the impact of introducing systematic algorithms in diagnosis and treatment, specifically for depressed inpatients. It also intends to elucidate the factors influencing medical decision making in the complex clinical reality (true world).[43] Phase 3 of the Berlin Algorithm Project is supposed to generate data that allow a comparison of algorithm-guided stepwise treatment procedures between a United States and a German population. This ongoing multicenter phase 3 algorithm study evaluates 2 different algorithms and different strategies in nonresponders to an initial antidepressant monotherapy.

Guidelines and treatment algorithms are increasingly important given the growth of treatment options and treatment facilities on the one hand, and the economic pressure impacting the public health system on the other. The evidence-based medicine concept defines standards in psychiatry against which treatment strategies have to be evaluated.[44–46] It is thus of major importance to evaluate not only the efficacy of particular agents or treatment strategies, but also existing therapeutic guidelines. This goal can be achieved only if the effectiveness and efficacy of a guideline-driven and algorithm-based complex treatment procedure is scientifically proved.[47]

Algorithm developers must be aware of the potential risks in the development and implementation of systematic treatment algorithms. Examples of the hazards of algorithm formulation are insufficient evidence, biased opinions, or inappropriate application by administrators and users.[40] Despite the potential risks, the introduction of a systematic treatment algorithm may enhance treatment quality, even for excluded patients. This enhancement may result when physicians develop alternative treatment strategies for patients upon deciding to exclude them, thus leading to a more coherent medical decision-making process.[17,47] Proper training and education of the physicians who will use the algorithm are important issues. Implementation of a treatment algorithm in a clinical setting requires the physician to decide on how to match standardized treatment rules with the individual needs of a particular patient. The study presented here was designed to explore the acceptance and adherence of a presented algorithm in a group of physicians who were not specifically trained to comply with systematic algorithm-guided decision making prior to the beginning of the study. This may have contributed to the high number of excluded patients in this study, which could be interpreted as a suboptimal acceptance of the SSTR. In contrast, adherence to the algorithm-based treatment rules was satisfactory once a patient was enrolled into the SSTR protocol; the latter effect could be attributed to regular supervision by the attending ward psychiatrists.

The present study has shown the overall moderate acceptance of the SSTR algorithm, as well as its favorable feasibility and effectiveness under conditions of an open, observational design in typical inpatients of a psychiatric university hospital who are frequently characterized as having an unfavorable treatment outcome.[1,2] We assume that the acceptance of a treatment algorithm can be optimized by providing specific instructions to the algorithm users. The goal of the present study was not to obtain conclusions on the efficacy of an algorithm-guided antidepressive treatment compared with "standard treatment as usual." Only a study with a randomized controlled design can prove that an algorithm-guided treatment procedure results in higher efficacy in terms of treatment outcome and treatment duration to remission and leads to a more efficient and economic use of medication and treatment strategies.[37]

Drug names: amitriptyline (Elavil, Endep, and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Carbatrol, and others), clomipramine (Anafranil), haloperidol (Haldol and others), nortriptyline (Pamelor, Aventyl, and others), tranylcypromine (Parnate).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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