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REGULAR RESEARCH ARTICLE

How Effective Is Algorithm-Guided Treatment for Depressed Inpatients? Results from the Randomized Controlled Multicenter German Algorithm Project 3 Trial

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Abstract

Background: Treatment algorithms are considered as key to improve outcomes by enhancing the quality of care. This is the first randomized controlled study to evaluate the clinical effect of algorithm-guided treatment in inpatients with major depressive disorder.

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Significance Statement

Providing algorithm-guided antidepressive treatments is considered an important strategy to optimize treatment delivery and avoid or overcome treatment-resistant courses of major depressive disorder (MDD), still a major challenge in the treatment of depression. The clinical benefit of algorithms in the treatment of inpatients with MDD had not been investigated in a large-scale, randomized, controlled trial before. The aim of the German Algorithm Project therefore was to evaluate the effects of treatment algorithms in the care of inpatients with MDD. Results show that a stepwise treatment regimen with critical decision points at the end of each treatment step based on standardized measurements of response and an algorithm-guided decision-making process increases the chance of achieving remission and optimizes prescription behaviors for antidepressants.

Methods: Inpatients, aged 18 to 70 years with major depressive disorder from 10 German psychiatric departments were randomized to 5 different treatment arms (from 2000 to 2005), 3 of which were standardized stepwise drug treatment algorithms (ALGO). The fourth arm proposed medications and provided less specific recommendations based on a computerized documentation and expert system (CDES), the fifth arm received treatment as usual (TAU). ALGO included 3 different second-step strategies: lithium augmentation (ALGO LA), antidepressant dose-escalation (ALGO DE), and switch to a different antidepressant (ALGO SW). Time to remission (21-item Hamilton Depression Rating Scale ≤9) was the primary outcome.

Results: Time to remission was significantly shorter for ALGO DE (n = 91) compared with both TAU (n = 84) (HR = 1.67; $P = .014$) and CDES (n = 79) (HR = 1.59; $P = .031$) and ALGO SW (n = 89) compared with both TAU (HR = 1.64; $P = .018$) and CDES (HR = 1.56; $P = .038$). For both ALGO LA (n = 86) and ALGO DE, fewer antidepressant medications were needed to achieve remission than for CDES or TAU ($P < .001$). Remission rates at discharge differed across groups; ALGO DE had the highest (89.2%) and TAU the lowest rates (66.2%).

Conclusions: A highly structured algorithm-guided treatment is associated with shorter times and fewer medication changes to achieve remission with depressed inpatients than treatment as usual or computerized medication choice guidance.

Keywords: treatment algorithms, antidepressants, treatment-resistant depression, medical decision making, German Algorithm Project

Introduction

About 30% to 40% of patients with major depressive disorder (MDD) do not respond to their first medication trial. More than one-half of these nonresponders do not respond to a second treatment step (Fava and Rush, 2006; Rush et al., 2006; Trivedi et al., 2006b). Even among those who respond, up to 50% maintain residual symptoms (Frank et al., 1991; Greden, 2001; Bauer et al., 2013), which increases the risk of relapse and chronicity (Paykel et al., 1995; Bauer et al., 2013, 2015; Bschor et al., 2014).

Treatment algorithms are regarded as key instruments to optimize treatment delivery and outcomes. These explicit treatment protocols aim at a predefined treatment goal (e.g., remission or response). The major procedural elements of treatment algorithms are strategies (which treatments to use), tactics (how to implement the treatments), treatment steps (in what order to implement the different treatments), standardized evaluation instruments, and critical decision points (CDPs). At CDPs, treatment outcome is assessed and a standardized medical decision is derived based on preset "if-then-rules" (Rush et al., 1998; Adli et al., 2003). A review of 24 depression disease management programs including treatment algorithms revealed a significant improvement in depressive symptoms, significantly greater patient satisfaction, and better compliance with treatment but also increased healthcare costs (Badamgarav et al., 2003) compared with treatment as usual (TAU). However, a large-scale multicenter study to evaluate an algorithm-guided treatment of depressed inpatients has not yet been performed.

The multi-phase German Algorithm Project (GAP) aims to evaluate the efficacy, acceptability, and impact on treatment quality of algorithm-guided depression treatment (Adli et al., 2003). An open observational 2-year single-center pilot study (GAP1) suggested reasonable clinical effectiveness and feasibility of a standardized stepwise drug treatment regimen in depressed inpatients (Adli et al., 2002). GAP2, a single-center randomized trial, found algorithm-guided treatment was associated with significantly higher remission rates and greater treatment quality than TAU (Bauer et al., 2009).

The GAP3 study presented here is a multicenter trial conducted within the German Research Network on Depression that included 6 academic and 4 nonacademic psychiatric hospitals. GAP3 compared 2 different treatment assistance approaches: the standardized stepwise drug treatment algorithm (ALGO) and a computerized decision and expert system (CDES) that recommends medications based on the patient's individual medication history and regular reminders to change or maintain the treatment based on the current response pattern. Both approaches, which will be described in detail in the Methods section (study design), were compared to TAU in terms of treatment efficacy, treatment quality, tolerability, and acceptance of treatment.

We hypothesized that algorithm-guided treatment results in superior outcomes compared with TAU. In addition, we aimed to compare outcomes of the highly schematic ALGO and the partially individualized CDES. Within the 3 ALGO groups, 3 arms compared different second-step strategies (lithium augmentation; ALGO LA), dose escalation of the initial substance (ALGO DE), and switch to another antidepressant (ALGO SW) in nonresponders to an initial medium-dose antidepressant monotherapy.

Methods

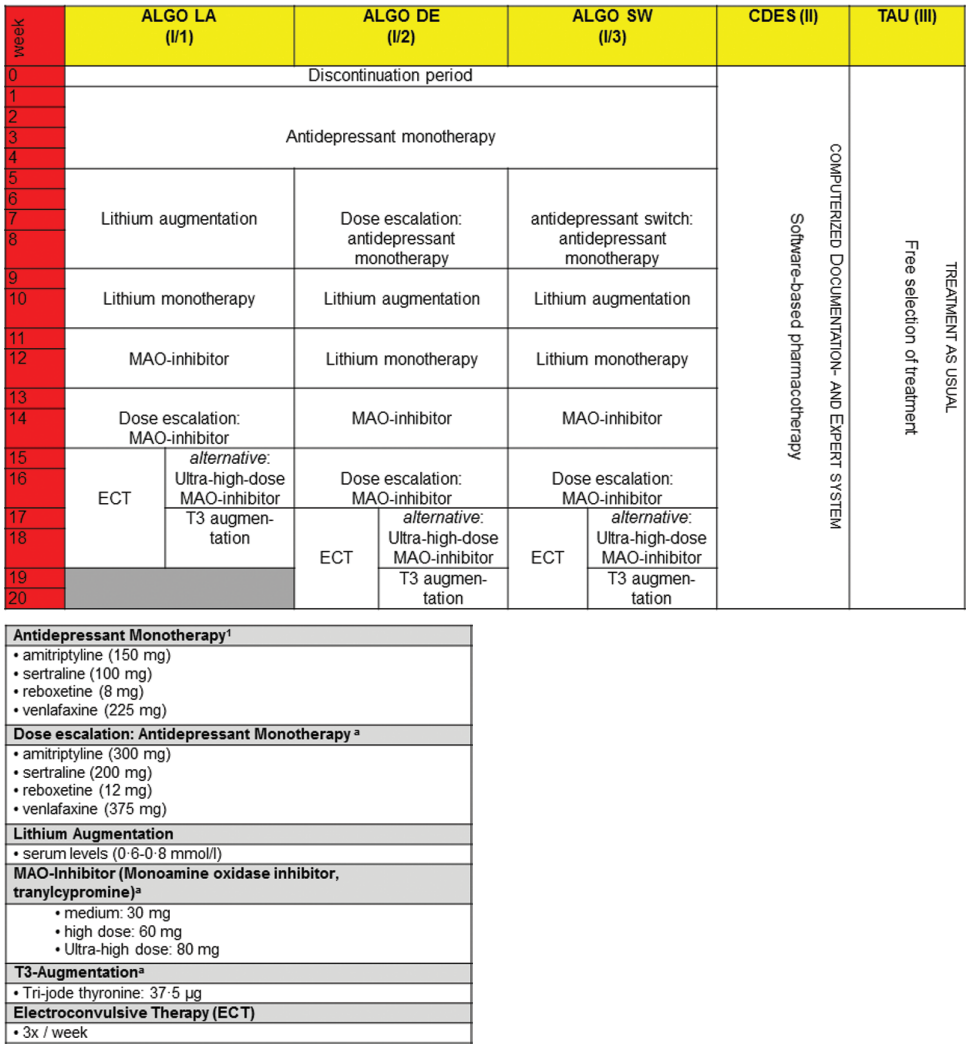
This randomized controlled parallel-designed clinical multicenter GAP3 trial, conducted between 2000 and 2005, was part of a naturalistic study (Seemuller et al., 2010) that described the outcomes of all depressed inpatients from admission to discharge with the primary diagnosis of a major depressive episode according to ICD-10.

Participants

Adult inpatients (aged 18–70 years) with a current major depressive episode (unipolar, with or without psychotic symptoms, but not with bipolar depression) and a 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton, 1960; Williams, 1988) score of ≧15 were study eligible. Exclusion criteria were: pregnancy or breastfeeding, preexisting psychotropic medication treatment that could not be discontinued, and specific medical conditions that presented a limitation for any possible study treatment (e.g., renal insufficiency as a limitation for lithium). All patients admitted to each participating center were systematically assessed for eligibility. Each local ethical committee approved and monitored the study. All study participants provided written informed consent.

Study Design

Figure 1 summarizes the study design. Upon enrollment, patients were equally randomized into 5 treatment groups. Within the 3 ALGO groups, all participants began with any 1 of 4 different antidepressants chosen to represent common pharmacological classes: (selective-serotonin-reuptake-inhibitor) sertraline; (serotonin-noradrenalin-reuptake-inhibitor) venlafaxine; (selective-nor-adrenaline-reuptake-inhibitor) reboxetine; (tricyclic antidepressant) amitriptyline. The second steps represent 3 different common next step strategies (ALGO LA, ALDO DE, or ALGO SW) that could be taken when nonresponse to the first step (4-week medium dose antidepressant monotherapy) occurred. For this report, we label each pathway by the second step itself. The subsequent steps in ALGO also differed as depicted in Figure 1. ALGO mandated further strategies based on prior responses to each step. For ALGO LA, serum levels were assessed weekly (target dose 0.6–0.8 mmol/L) (Bauer et al., 2013). As part of the ALGO procedure, the HAMD-21 score difference



Antidepressant Monotherapy[1]
• amitriptyline (150 mg) • sertraline (100 mg) • reboxetine (8 mg) • venlafaxine (225 mg)
Dose escalation: Antidepressant Monotherapy [a]
• amitriptyline (300 mg) • sertraline (200 mg) • reboxetine (12 mg) • venlafaxine (375 mg)
Lithium Augmentation
• serum levels (0·6-0·8 mmol/l)
MAO-Inhibitor (Monoamine oxidase inhibitor, tranylcypromine)[a]
• medium: 30 mg • high dose: 60 mg • Ultra-high dose: 80 mg
T3-Augmentation[a]
• Tri-jode thyronine: 37·5 µg
Electroconvulsive Therapy (ECT)
• 3x / week

Figure 1. Overview of the study design. ALGO, standardized stepwise drug treatment algorithm; ALGO DE, ALGO pathway with dose escalation; ALGO LA, ALGO pathway with lithium augmentation; ALGO SW, ALGO pathway with antidepressant switch; CDES, computerized documentation and expert system; ECT, electroconvulsive therapy; MAO-inhibitor, monoamine oxidase inhibitor; TAU, treatment as usual. The indicated doses refer to doses per day.

between the beginning and the end of each 4-week step was used to ascribe remission, partial response, or nonresponse as the outcome. Remission was declared with a HAMD-21 ≤9. Remission was to be confirmed in a retest after 2 weeks. If recurrence was observed, the patient either received a 2-week prolongation of the specific treatment step (if HAMD-21 = 10–14) or directly moved to the next step (if HAMD-21 was ≥15).

If partial response occurred (defined as a score reduction of >8 or >30% without achieving remission), a 2-week prolongation of the current treatment step was allowed (only once per step). Nonresponse was defined as not meeting remission or partial response criteria. These patients moved to the next treatment step.

CDES used individual patients' information, prior treatment history, risk factors, and responses to the current treatment with a probability matrix to generate suggestions based on a clinical data pool derived from treatment courses of 650 patients with MDD (Laakman et al., 1995; Faltermaier-Temizel et al., 1997). The software calculated the probability of an individual patient's response every 2 weeks based on the HAMD-21 score. If response was determined to be likely, the system recommended maintaining the strategy. In cases of unlikely responses, the software recommended changing the current strategy but in a more general way (e.g., "consider augmentation or switch to another compound"). In addition, CDES provided an overview of past treatments and listed previous treatments associated with response or nonresponse or side effects in each patient (for additional information please see Appendix 1). The fifth group received TAU.

Measures

A systematic interview (Cording, 1995) captured baseline clinical and socio-demographic features of the sample. Clinical diagnoses were confirmed with the Structured Clinical Interview for DSM-IV (Wittchen, 1997). The Structured Clinical Interview-II assessed comorbid personality disorders (Wittchen, 1997).

In all 5 groups, treatment outcome was assessed every 2 weeks (±3 days) by nonmasked research staff who were uninvolved in treatment. The primary outcome based on the HAMD-21 was time to remission (HAMD-21 ≤9).

Secondary outcomes included dropout rates and treatment process parameters for each group (e.g., number of strategy changes, ascribed when a new medication was added or discontinued; total number of psychotropic medications, number of different pharmacological drug classes).

Medication doses were calculated as defined drug doses, the assumed average maintenance dose per day for a medication used for its main indication in adults (WHO, 2003). We used the recommendations in the Antidepressant Treatment History Form to define adequate doses of antidepressants (Sackeim, 2001) based on the minimal dosage at which randomized controlled trials have shown the agent to be effective in major depression. Dropout reasons were withdrawal of consent, discharge or transfer to another hospital (patient's or doctor's choice) before remission or final rating, protocol violations, side effects, or suicide (supplementary Table 1). Patients from TAU were rated as dropouts in case of withdrawal of consent, premature discharge, or suicide.

Concomitant Treatments

Modest concomitant medication restrictions were placed on patients in ALGO. Lorazepam and non-benzodiazepine hypnotics (zopiclone and zolpidem) were permitted for agitation, anxiety, or sleeping problems. In psychotic depression, risperidone (up to 4 mg/d) or olanzapine (up to 15 mg/d) were allowed as co-medication.

Randomization and Masking

Randomization was performed in blocks of 10, separately for each study site, and random figures were generated using www.randomizer.org. Study staff and patients were masked to the randomization code until inclusion assessment was finished. Thereafter, patients, physicians, and outcome assessors were not blinded to the treatment allocation.

Statistical Analysis

The sample size estimate of 450 participants was based on the primary outcome variable: time to remission. Assumptions were a variance of 4 weeks and a mean difference of 2 weeks between groups was used a priori to define clinical relevance. This is equivalent to an effect size of d = 0.50, and power would be 0.80. To account for dropouts, 90 patients had to be enrolled per study group.

SPSS (Statistical Package for Social Science) version 18.0 was used for statistical operations. Calculations were performed with SAS version 6.12 for Windows NT and UnifyPow. Differences in baseline or treatment characteristics between the groups (ALGO groups, CDES, and TAU) were assessed using a chi-squared test or logistic regression for categorical variables and an ANOVA for continuous variables. With an alpha error of 5%, statistical significance for all analyses was assumed with $P < .05$ (2-tailed). Survival analysis was conducted to be able to use all patient data including right-censored cases due to dropout events. It was assumed that treatment response did not differ between patients remaining in the study until remission and dropout. Median survival times were calculated using Kaplan-Meier statistics. Differences in time to remission were analyzed using Cox Regression Modeling. Model comparison was based on the likelihood ratio test (LRS). Of primary interest was an overall difference between groups. This was evaluated using the likelihood ratio test. All other comparisons were performed exploratively and thus no type I error adjustment was performed.

Results

Of 593 patients who entered the naturalistic study (Seemuller et al., 2010) between 2000 and 2005, 475 (80.1%) enrolled in GAP3 at 10 sites (see Acknowledgments). Of these 475 patients, 429 were eligible for further analysis (Figure 2). Table 1 shows the baseline characteristics of the study sample.

Time to Remission

Cox regression survival analysis showed a significant difference in median time to remission between groups (42 [95% CI 30.95–53.05] days for ALGO LA, 37 [Cl 28.36–45.64] days for ALGO DE, 40 [95% Cl 29.21–50.79] days for ALGO SW, 45 [95% Cl 32.74–57.25] days for CDES vs 45 [95% Cl 32.09–57.91] days for TAU, likelihood ratio test = 11.078, $P = .026$). Compared with TAU, subsequent Cox regression analysis showed that the probability for remission was significantly higher for ALGO DE (HR = 1.67 [95%CI 1.11–2.52] Wald test = 6.03, $P = .014$) and for ALGO SW (HR = 1.64 [95%CI 1.10–2.48] Wald test = 5.60, $P = .018$), but narrowly missed statistical significance for ALGO LA (HR = 1.49 [95%CI 0.99–2.25] Wald test = 3.69, $P = .055$), while there was no difference for time to remission between CDES and TAU (HR = 1.06 [95% CI 0.68–1.63],

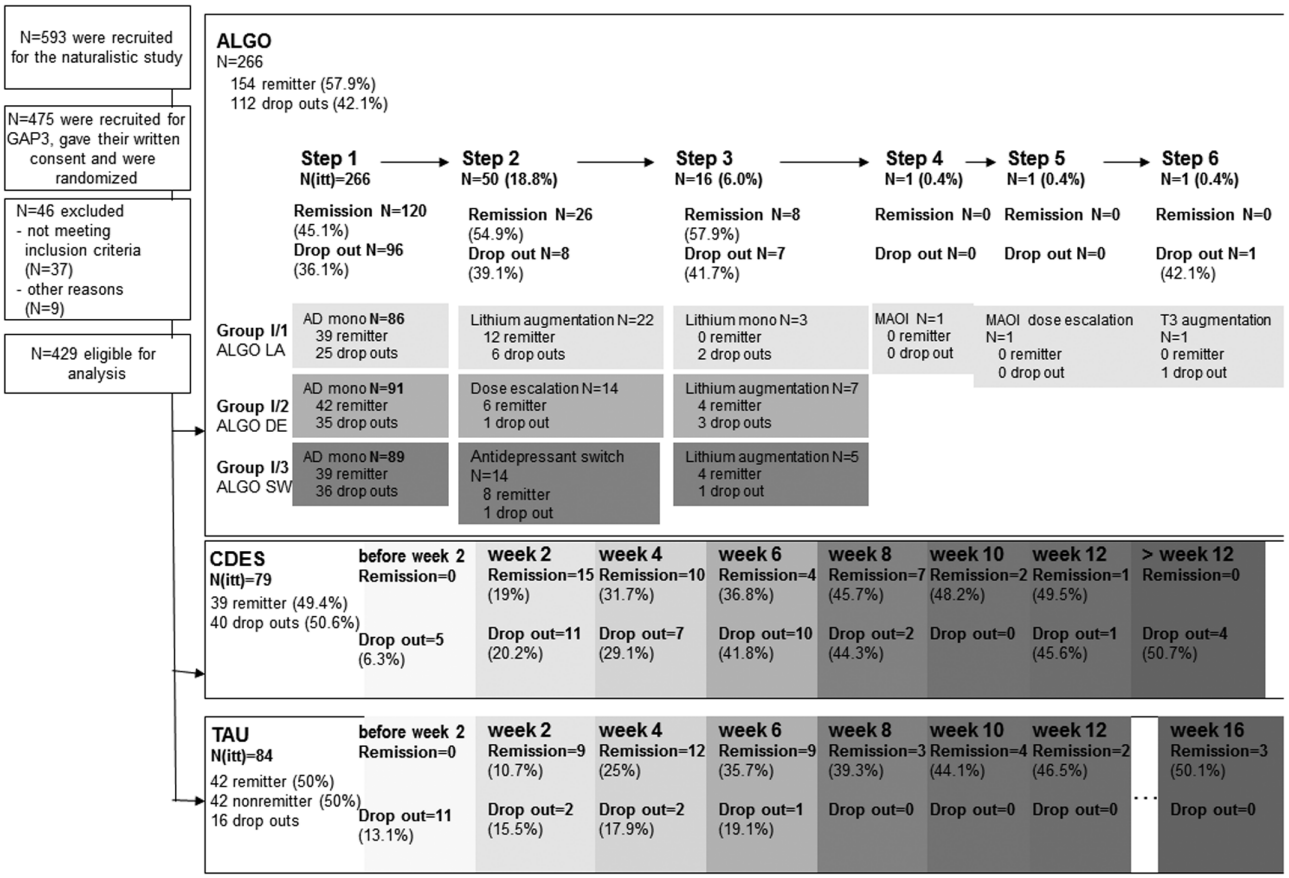


Figure 2. Overview of remission and dropouts in the study groups and throughout the ALGO pathways. AD mono, antidepressant monotherapy; ALGO, standardized stepwise drug treatment algorithm; ALGO DE, ALGO pathway with dose escalation; ALGO LA, ALGO pathway with lithium augmentation; ALGO SW, ALGO pathway with antidepressant switch; CDES, computerized documentation and expert system; GAP3, German Algorithm Project phase 3; MAOI, monoamine oxidase inhibitor; T3, trijodthyronine; TAU, treatment as usual.

Wald test = 0.06, $P = .811$) (HR = 1.06 [95% CI 0.68–1.63], Wald test = 0.06, $P = .811$). Compared with CDES, probability for remission was significantly higher for ALGO DE (HR = 1.59 [95% CI 1.04–2.41] Wald test = 4.64, $P = .031$), for ALGO SW (HR = 1.56 [95%CI 1.03–2.37] Wald = 4.30, $P = .038$), but not for ALGO LA (HR = 1.42 [95%CI 0.93–2.15] Wald test = 2.66, $P = .103$) (Figure 3).

Remission and Dropout Analysis

Of 429 patients, 235 (54.8%) achieved remission and 276 (64.3%) achieved response during the study (reduction of HAMD-21 score ≥50%). Remission or response rates during the study and time in hospital were not different between the 5 groups (Table 2).

Overall, 169/429 (39.4%) dropped out of the study protocol for various reasons (see supplementary Table 1). Dropouts were less frequent in TAU (19%) than in each of the 3 ALGO pathways: ALGO LA (40.7%), ALGO DE (42.9%), ALGO SW (42.7%), as well as CDES (50.6%) (chi-square = 19.70; $P = .001$).

Figure 2 provides an overview of remission and dropout rates per step or per week. Within ALGO, most of the remissions (45.1% of the intention-to-treat [ITT] sample, 77.9% of remitted patients) and most of the dropouts (36.1% of ITT sample, 85.7% of dropouts) occurred during the first (antidepressive monotherapy) step. In the second and third steps, another 9.8% and 3%, respectively, of the initial sample achieved remission. In CDES, most of the remissions (64.1% of remitted patients, 31.6% of ITT sample) and of dropouts (57.5% of dropouts, 29.1% of ITT sample) occurred during the first 4 weeks of treatment. In TAU, 50% of final remitters remitted during the first 4 weeks of treatment (25% of ITT sample).

Status at Discharge

At hospital discharge, HAMD-21 data were available for 318/429 (74.1%) of participants of whom 245/318 (77%) were remitted. A total of 76.6% of patients from the ALGO LA pathway were remitted compared with 89.2% of patients from ALGO DE, 85.5% from ALGO SW, 67.7% from CDES, and 66.2% from TAU (chi-square = 15.36, $P = .004$).

Treatment Features

Complete medication data were available for 350 patients. The subgroup analysis of those patients who achieved remission (n = 217) showed that patients in ALGO LA and ALGO DE needed fewer different kinds of antidepressants than patients in either CDES or TAU (Table 3), even when taking into account time to remission in an ANCOVA.

Of remitters, (n = 217) 46.5% received hypnotics. CDES patients were more likely to be prescribed hypnotics than TAU patients (OR = 3.95 [95 % CI 1.51–10.34], $P = .005$), but not patients in the ALGO pathways (Table 3).

Until remission, 12% of the patients (26/217) were treated with antidepressant doses below the minimal effective dose in

Table 1. Baseline Characteristics of Study Sample

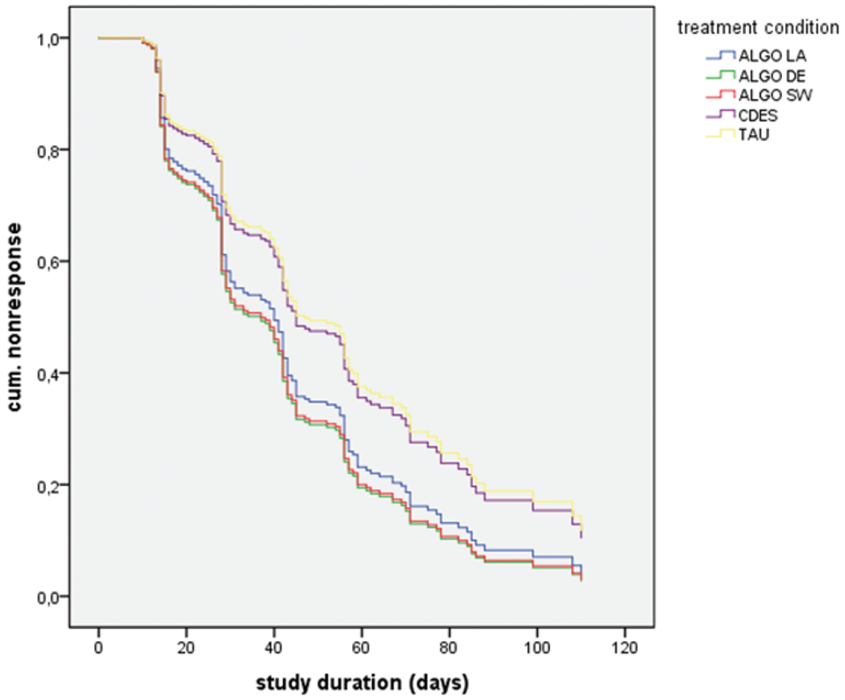
	ALGO LA	ALGO DE	ALGO SW	CDES	TAU	Statistic	P
Sample size	86	91	89	79	84		
Female (%) n = 428	65.9	62.6	62.9	74.7	51.2	$Chi^2 = 9.978$	.041
Age (years: M, sd) n = 429	45.6 ± 11.1	44.3 ± 13.3	42.2 ± 13.4	43.6 ± 12.5	45.1 ± 11.7	F = 1.012	.401
Married / partnership (%) n = 397	45.0	34.9	44.6	38.9	38.2	$Chi^2 = 2.619$	.623
Number of children (M, sd) n = 356	1.3 ± 1.1	1.1 ± 1.3	1.1 ± 1.1	1.0 ± 1.0	1.1 ± 1.1	F = 0.724	.576
Employed (full- or part-time) (%) n = 385	45.1	32.1	55.7	33.8	36.1	$Chi^2 = 12.526$	.014
High school diploma (%) n = 389	26.6	31.0	36.6	27.8	25	$Chi^2 = 3.187$	.527
any school qualification (%) n = 389	92.4	97.6	96.3	90.3	98.6	$Chi^2 = 8.169$	.086
Vocational qualification (%) n = 388	71.3	75.3	81.0	81.4	86.5	$Chi^2 = 6.507$	.164
Depressive Episode, single (%) n = 420	53.6	40.0	59.8	37.7	42.7	$Chi^2 = 12.232$	.016
Psychotic symptoms (%) n = 420	10.7	5.6	8.0	5.2	3.7	$Chi^2 = 4.117$	.390
Depression severity at baseline (HAMD-21 score; M, sd) n = 429	25.9 ± 6.5	25.4 ± 5.3	25.4 ± 5.8	25.6 ± 6.0	27.4 ± 6.3	F = 1.668	.156
Duration of current episode (weeks; M, SD) n = 246	20.8 ± 31.3	13.6 ± 15.4	15.9 ± 14.8	29.5 ± 73.7	18.6 ± 24.7	F = 1.280	.278
Duration since illness onset (years; M, SD) n = 262	5.8 ± 8.5	8.8 ± 10.7	5.5 ± 9.4	10.4 ± 13.0	8.3 ± 8.2	F = 2.229	.066
Total number depressive episodes, including current episode (M, SD) n = 251	2.3 ± 2.1	2.7 ± 2.9	1.8 ± 1.4	2.4 ± 1.7	2.8 ± 2.4	F = 1.660	.160
Comorbidity							
Psychiatric (%) n = 420	27.1	24.7	20.7	22.1	24.4	$Chi^2 = 1.145$	.887
Personality disorder (%) n = 429	5.8	12.1	10.1	8.9	8.3	$Chi^2 = 2.282$	.684

ALGO: standardized stepwise drug treatment algorithm; ALGO LA: ALGO pathway with lithium augmentation; ALGO DE: ALGO pathway with dose escalation; ALGO SW: ALGO pathway with antidepressant switch; HAMD: Hamilton Rating Scale for Depression; BDI: Beck Depression Inventory; CDES: computerized documentation and expert system, TAU: treatment as usual.

at least one of the prescribed antidepressants. The risk of being treated with insufficiently dosed antidepressants was significantly higher in CDES than TAU (OR = 6.00 [95% CI 1.18–30.53], *P* = .031), whereas patients in the 3 ALGO pathways were at significantly lower risk compared with CDES (ALGO LA (OR = 0.15 [95% CI 0.03–0.75], *P* = .021), in ALGO DE (OR = 0.144 [95% CI 0.03–0.73], *P* = .019), and in ALGO SW (OR = 0.14 [95% CI 0.03–0.70], *P* = .017). There was no significant difference between ALGO groups and TAU.

Discussion

Study results indicated that algorithm-guided treatment of depression (ALGO) is generally associated with a shorter time to



	Wald	Hazard-Ratio	p
ALGO LA vs. TAU	3·69	1·49	0·055
ALGO DE vs. TAU	6·03	1·67	0·014
ALGO SW vs. TAU	5·60	1·64	0·018
CDES vs. TAU	0·06	1·06	0·811

Figure 3. Time to remission for standardized stepwise drug treatment algorithm (ALGO) pathway with lithium augmentation (ALGO LA), ALGO pathway with dose escalation (ALGO DE), ALGO pathway with antidepressant switch (ALGO SW), computerized documentation and expert system (CDES), and treatment as usual (TAU).

remission than either an individualized CDES or TAU. Probability of achieving remission was significantly higher for ALGO DE and ALGO SW but narrowly failed statistical significance for ALGO LA. Dropout rates are relatively high in all 3 ALGO pathways and less frequent in TAU. ALGO-treated patients who dropped out of the protocol still maintained a higher probability of leaving the hospital in remission than patients in CDES or TAU, although durations of inpatient treatment did not differ between the groups.

We found more insufficient dosing of antidepressants and prescription of hypnotics in CDES and higher numbers of antidepressants used to achieve remission in TAU and CDES groups than for either ALGO LA or ALGO DE pathways.

These findings are in line with our single site GAP2 project (Bauer et al., 2009), which demonstrated superior clinical outcomes of a similar standardized step-wise treatment algorithm compared with TAU. In contrast, however, the present study did not find that any of the ALGO pathways were associated with fewer strategy changes or less polypharmacy than TAU to achieve remission.

The efficacy of algorithm-guided depression treatments has been shown in several smaller studies and large-scale multi-site projects in different outpatient settings. The Texas Medication Algorithm Project found a superior overall treatment outcome and fewer side effects for patients being treated with a guided medication treatment algorithm (Trivedi et al., 2004). A more recent Japanese study reported a 10% higher remission rate for algorithm-treated patients following a stepwise treatment procedure compared with TAU (Yoshino et al., 2009). A recent randomized controlled study from China showed that measurement-based care, that is, the use of a symptom-rating scale, together with a dosing schedule showed superior outcomes compared with TAU even if medication and dose ranges did not differ between groups (Guo et al., 2015). Controlled studies and open trials in geriatric populations also showed the feasibility and effectiveness of intensive managed care programs (Flint and Rifat, 1996; Hawley et al., 1998; Mulsant et al., 2001; Unutzer et al., 2002; Bruce et al., 2004; Alexopoulos et al., 2005). The Sequenced Treatment Alternatives to Relieve Depression study evaluated a measurement-based, stepwise treatment approach in a large outpatient sample with nonpsychotic MDD (Rush et al., 2006; Trivedi et al., 2006a). However, the study failed to show the superiority of any of the compared escalation strategies (different augmentation, combination, or switch strategies) in nonresponders.

Notably, in this study, only a highly schematized algorithm-guided procedure resulted in superior outcomes but not an individualized software-based treatment assistance. This finding supports a major theory in algorithm research that diligent treatment management with a highly structured measurement-based procedure accounts for the difference in treatment outcomes rather than the application of a particular treatment

Table 2. Remission and Response[a]

	ALGO LA	ALGO DE	ALGO AS	CDES	TAU	statistic	P
Remission (n, %)	51 (59.3)	52 (57.1)	51 (57.3)	39 (49.4)	42 (50)	$chi^2 = 2.853$	.583
Response (n, %)	54 (62.8)	57 (62.6)	59 (66.3)	45 (57)	61 (72.6)	$chi^2 = 4.736$	.315
Total time in hospital (d)							
Completer (M, SD)	50.5 (28.6)	53.4 (25.3)	55.9 (34.3)	49.3 (26.1)	52.4 (29.7)	F = 0.183	.833
Total sample (M, SD)	53.6 (37.1)	55.6 (34.1)	55.4 (42.2)	58.6 (45.6)	50.6 (32.5)	F = 0.363	.835

Abbreviaitons: ALGO, standardized stepwise drug treatment algorithm; ALGO DE, ALGO pathway with dose escalation; ALGO LA, ALGO pathway with lithium augmentation; ALGO SW, ALGO pathway with antidepressant switch; CDES, computerized documentation and expert system; TAU, treatment as usual.
[a]Remission (HAMD-21≤9), response (reduction of HAMD-21 score ≥50%) during study duration and time in hospital for ALGO.

Table 3. Characteristics of Pharmacological Treatment

	ALGO LA	ALGO DE	ALGO AS	CDES	TAU		
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P
Number of antidepressants	1.00 (0.00)	1.00 (0.00)	1.22 (0.42)	1.29 (0.58)	1.29 (0.46)	7.21	.000
Defined daily doses (DDD) of antidepressants	61.09 (42.03)	69.62 (59.85)	57.94 (36.73)	61.59 (59.06)	80.15 (71.51)	1.16	.329
Treatment duration with 1st antidepressant (d)	31.22 (18.36)	31.40 (18.72)	27.41 (11.99)	31.26 (19.84)	34.21 (20.85)	0.83	.510
Number of different pharmacological drug classes	2.54 (1.09)	2.57 (1.14)	2.47 (0.92)	2.76 (1.02)	2.44 (1.18)	0.53	.716
Number of strategy changes	1.59 (0.88)	1.68 (1.09)	1.98 (1.55)	1.97 (1.57)	2.20 (1.75)	1.38	.241
Number of hypnotics	0.72 (1.07)	0.62 (0.82)	0.59 (0.79)	0.76 (0.65)	0.41 (0.67)	1.07	.372
Defined daily doses (DDD) of hypnotics	8.31 (17.26)	9.04 (14.92)	16.45 (53.83)	11.11 (18.06)	7.49 (18.36)	0.69	.599
Treatment duration with hypnotics (d)	7.70 (12.03)	8.96 (14.06)	10.12 (18.74)	11.56 (16.89)	6.95 (14.49)	0.56	.689
Number of tranquilizer	0.63 (0.57)	0.60 (0.54)	0.67 (0.47)	0.74 (0.57)	0.56 (0.55)	0.61	.653
Defined daily doses (DDD) of tranquilizer	4.41 (7.55)	7.98 (15.16)	9.41 (15.89)	6.92 (12.05)	9.64 (19.16)	0.97	.423
Treatment duration with tranquilizer (d)	7.20 (10.92)	8.91 (14.06)	11.14 (16.13)	9.29 (14.26)	9.32 (14.89)	0.47	.760
Number of Antipsychotics	0.28 (0.72)	0.49 (0.83)	0.37 (0.67)	0.35 (0.65)	0.27 (0.67)	0.69	.601
Defined daily doses (DDD) of antipsychotics	3.20 (10.35)	8.35 (19.05)	5.08 (15.68)	4.12 (11.94)	6.15 (25.42)	0.59	.669
Treatment duration with antipsychotics (d)	4.46 (11.98)	8.93 (16.42)	4.88 (11.99)	4.53 (11.22)	7.29 (23.03)	0.74	.563

Abbreviations: ALGO, standardized stepwise drug treatment algorithm; ALGO AS, ALGO pathway with antidepressant switch; ALGO DE, ALGO pathway with dose escalation; ALGO LA, ALGO pathway with lithium augmentation; CDES, computerized documentation and expert system; TAU, treatment as usual.
DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults; each new prescription and each discontinuation was considered a strategy change.

strategy per se (Adli et al., 2006; Rush, 2015). A more individualized treatment guidance that lacks clear-cut treatment strategies and without explicit "if-then" rules is not different from TAU and, therefore, might not be cost effective. In contrast, we even found a higher rate of insufficiently dosed antidepressants in CDES, which might also explain the lower remission and response rates in this group compared with ALGO (Rush, 2015). This finding shows that algorithms also bear the risk of decrementing treatment processes.

Our results show a shorter time to remission for ALGO DE and ALGO SW but only a nonsignificant trend for ALGO LA compared with CDES and TAU. We had expected lithium augmentation to prove more effective than dose escalation or switch of antidepressant with regard to the broad basis of evidence in favor of this strategy (Crossley and Bauer, 2007). However, interpretation of our second step results has to be done with caution due to the low number of patients in this study step and insufficient statistical power.

Future studies need to address the question of the appropriate timing of CDPs and different response categories that result in specific operational consequences in a specific clinical environment (outpatients, inpatients, characteristics of health system). The question of which treatment sequences are preferred for particular subpopulations (e.g., stage of treatment resistance, age, presence of psychiatric and nonpsychiatric comorbidities) needs clarification. Before implementation into clinical practice, algorithm developers must ensure feasibility and clinical efficacy of a treatment algorithm in a particular treatment environment and applicability to patient subgroups, as demonstrated by our CDES results.

Study limitations include: the lack of power in all 3 algorithm-guided treatment steps after step one, primarily due to a high remission rate during antidepressant monotherapy. In addition, the study team, clinical staff, and patients were not masked to treatment assignment, which could have led to a bias in favor of the ALGO groups. However, response assessments were performed by staff that was not involved in the treatment of the patient. A conservative bias results from the fact that the same clinicians who treated ALGO and CDES patients also treated patients in TAU, which is expected to result in "contamination" of TAU with ALGO and CDES treatment procedures, thus reducing outcome differences between the groups. Also, differences in distribution of clinical or sociodemographic variables between the treatment groups (such as gender, type of depression [single vs recurrent], duration of the illness, or percentage of psychotic depression) could be of clinical relevance and therefore may weaken the interpretation of our results. As the dropout rate in TAU is lower than ALGO or CDES while 2 of the

ALGO groups did better in terms of time to remission, it cannot be ruled out that subjects doing poorly in ALGO or CDES dropped out whereas they stayed in the TAU group. However, as survival analysis regards dropouts as treatment failures such a bias seems unlikely to have influenced the result. Results are applicable only to inpatient populations. Inpatient stays in Germany are longer in average compared with the United States, which might limit generalizability. However, the German healthcare system has a relatively low threshold for hospital admission of depressed patients, so results would seem to be generalizable to the more severely ill depressed patients regardless of treatment venue.

In summary, these results demonstrate that an algorithm-guided treatment procedure that entails the regular measurement of outcomes and mandates next steps results in a higher probability of achieving remission and of leaving the hospital in remission than TAU. ALGO reduces the number of antidepressant compounds needed to achieve remission. In contrast, we showed that algorithms may also bear risks, as seen with CDES with its less clear recommendations, and therefore need to be evaluated before implementing them in clinical practice.

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