Texas Medication Algorithm Project, Phase 3 (TMAP-3): Clinical Results for Patients With a History of Mania

Trisha Suppes, M.D., Ph.D.; A. John Rush, M.D.; Ellen B. Dennehy, Ph.D.; M. Lynn Crismon, Pharm.D.; T. Michael Kashner, Ph.D., J.D., M.P.H.; Marcia G. Toprac, Ph.D.; Thomas J. Carmody, Ph.D.; E. Sherwood Brown, Ph.D., M.D.; Melanie M. Biggs, Ph.D.; Kathy Shores-Wilson, Ph.D.; Bradley P. Witte, B.S.; Madhukar H. Trivedi, M.D.; Alexander L. Miller, M.D.; Kenneth Z. Altshuler, M.D.; and Steven P. Shon, M.D.

Background: The Texas Medication Algorithm Project (TMAP) assessed the clinical and economic impact of algorithm-driven treatment (ALGO) as compared with treatment-as-usual (TAU) in patients served in public mental health centers. This report presents clinical outcomes in patients with a history of mania (BD), including bipolar I and schizoaffective disorder, bipolar type, during 12 months of treatment beginning March 1998 and ending with the final active patient visit in April 2000.

Method: Patients were diagnosed with bipolar I disorder or schizoaffective disorder, bipolar type, according to DSM-IV criteria. ALGO was comprised of a medication algorithm and manual to guide treatment decisions. Physicians and clinical coordinators received training and expert consultation throughout the project. ALGO also provided a disorder-specific patient and family education package. TAU clinics had no exposure to the medication algorithms. Quarterly outcome evaluations were obtained by independent raters. Hierarchical linear modeling, based on a declining effects model, was used to assess clinical outcome of ALGO versus TAU.

Results: ALGO and TAU patients showed significant initial decreases in symptoms ($p = .03$ and $p < .001$, respectively) measured by the 24-item Brief Psychiatric Rating Scale (BPRS-24) at the 3-month assessment interval, with significantly greater effects for the ALGO group. Limited catch-up by TAU was observed over the remaining 3 quarters. Differences were also observed in measures of mania and psychosis but not in depression, side-effect burden, or functioning.

Conclusion: For patients with a history of mania, relative to TAU, the ALGO intervention package was associated with greater initial and sustained improvement on the primary clinical outcome measure, the BPRS-24, and the secondary outcome measure, the Clinician-Administered Rating Scale for Mania (CARS-M). Further research is planned to clarify which elements of the ALGO package contributed to this between-group difference.

(J Clin Psychiatry 2003;64:370–382)

Received June 11, 2002; accepted Dec. 23, 2002. *From the Department of Psychiatry (Drs. Suppes, Rush, Dennehy, Brown, Biggs, Shores-Wilson, Trivedi, and Altshuler and Mr. Witte) and Academic Computing (Dr. Carmody), University of Texas Southwestern Medical Center, Dallas; Pharmacy Practice and Administration, University of Texas at Austin College of Pharmacy, Austin (Dr. Crismon); the Texas Department of Mental Health and Mental Retardation, Austin (Drs. Toprac and Shon); the Health Services Research and Development Service Research Career Scientist Program, Department of Veterans Affairs, and Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr. Kashner); and the Department of Psychiatry, University of Texas Health Science Center at San Antonio (Dr. Miller).*

Direct funding/support disclosure appears at the end of this article.

Results of this study were presented in part at the 39th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 12, 2000; the 154th annual meeting of the American Psychiatric Association, New Orleans, La., May 7, 2001; and the 40th annual meeting of the American College of Neuropsychopharmacology, Waikoloa, Hawaii, December 9–13, 2001.

Individual financial disclosure appears at the end of this article.

Corresponding author and reprints: Trisha Suppes, M.D., Ph.D., Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9070 (e-mail: trisha.suppes@utsouthwestern.edu).

Patients with a history of mania (BD) include those with a diagnosis of schizoaffective illness, bipolar type and bipolar I disorder. They comprise about 2% of the adult population in the United States[1,2] and an estimated 30% of the population served by the Texas Department of Mental Health and Mental Retardation.[3] These disorders are chronic with an early age of onset and infrequent periods of full remission. This recurrent and chronic illness significantly impacts individuals, families, society, and health care systems. The severity and persistence of functional and social impairment in many of these patients are clearly recognized.[4–8]

Relative agreement exists on the overall limited efficacy of long-term lithium monotherapy for many patients with a history of mania. Long-term follow-up studies reveal a 50% recurrence rate among those initially responsive to lithium,[9–12] while failure to take medication also leads to poor outcome.[13,14] For patients with more complicated courses of illness, including rapid cycling (15%–20% of patients with a history of mania) and/or

  © Copyright 2003 Physicians Postgraduate Press, Inc.

episodes of mixed states (estimated to be 30%–60%), medication combinations may be necessary to optimize stabilization.[15–18]

Published practice guidelines for the treatment of these patients have addressed both the acuity and chronicity of these disorders by including combinations of medications, despite the paucity of controlled clinical trials on their use in patients with mania. Consequently, the evidence for recommendations rests primarily on expert consensus, which recognizes that combination treatments are common practice. An examination of all treatment guidelines and algorithms originating from diverse sources including the Department of Veterans Affairs,[19] the Consensus Guideline Series,[20,21] American Psychiatric Association,[22] Canadian Network for Mood and Anxiety Treatments,[23,24] International Psychopharmacology Algorithm Project,[25,26] and the European Algorithm Project[27] reveals that all recommend the use of 2 medications by the second step of the treatment algorithms.[28] A gap has evolved between a recognized need and the available evidence from randomized controlled trials to address this population.[29]

As application of treatment algorithms expands, it is important to determine whether treatment response in psychiatric illnesses will, in fact, be improved through a systematic approach to clinical management. This question was the focus of the Texas Medication Algorithm Project (TMAP).[30–34] Patients from the public mental health sector are rarely represented in research trials, as they are severely and persistently mentally ill. Earlier work within the Texas public mental health system by the authors and others has demonstrated that, while these patients are severely ill, observable and sustained improvement can occur through the use of systematic treatment approaches.[7,35] The gap between efficacy and effectiveness studies, particularly for public mental health patients, creates an environment in which there is virtually no research to inform detailed treatment recommendations.[29] Additionally, due to administrative and cost constraints, it is common that public sector patients, despite potentially benefiting from the newest interventions, are often the last to receive them. Systematic trials of an algorithmic treatment approach for patients with a history of mania have not been conducted in other public or private mental health systems. However, earlier experience suggests a lack of uniformity in patient management and significant variation in medication treatment.[35] It was our a priori expectation that the use of a defined treatment algorithm in combination with enriched resources and a family and patient education package would provide additional benefit for patients, manifested in greater initial and sustained clinical improvement.

The results presented here are from TMAP Phase 3. The results of Phase 1 (development of the initial treatment algorithms for bipolar disorder) and Phase 2 (a 4-month feasibility trial) demonstrated feasibility and patient, physician, and clinical staff acceptability of a step-wise decision tree or algorithmic approach to medication treatment for patients with bipolar disorder.[34] Importantly, the treatment guidelines were revised in anticipation of TMAP Phase 3 and reflect research data and expert opinion in 1998. Additionally, no economic restrictions were placed on the inclusion of brand name or new generation medications.

TMAP is the first study to evaluate the clinical, functional, and economic impact of the use of an algorithm treatment package for outpatients with a history of mania in community mental health clinics. The primary focus of this study was clinical outcomes for patients receiving treatment-as-usual (TAU) in comparison with those receiving an algorithm-driven disease management program (ALGO), which provided treatment recommendations, access to the newest medications, a dedicated clinical coordinator, uniform documentation, and a patient and family education program. Study outcomes included multiple domains: symptoms, function, quality of life, side-effect burden, and use of alcohol and substances. Results are provided on the 12-month clinical outcomes of patients enrolled in ALGO versus TAU across Texas for the study period of March 1998 to April 2000. This article focuses on the primary clinical outcome for patients in the BD module. Additional data on use of medications, physician adherence, and cost analyses will be presented in future publications.

METHOD

Study Design

This multisite study compared the clinical benefits of using ALGO versus TAU in public mental health centers across Texas. Four clinics utilized ALGO for BD. Seven matched clinics in which no ALGO was implemented provided control patients. Clinics were matched for practice setting (rural/urban) and ethnicity. The study development and design are described in Rush et al.,[36] this issue. Briefly, the study was conducted in accordance with international guidelines for good clinical practice and the Declaration of Helsinki and was approved by institutional review boards at University of Texas Southwestern Medical Center and University of Texas, Austin. Patients provided written informed consent prior to participation in the study. After enrollment, patients completed baseline and quarterly assessments for at least 1 year with an independent rater not involved in treatment. Assessment domains included clinical symptoms, function, and side-effect burden, as well as utilization of health care from other public and private sources. This study assigned conditions (e.g., ALGO or TAU) to clinics that were selected based upon predetermined criteria including number of patients served, stable administrative infrastructure, and ethnic and geographic diversity, as well as other variables.

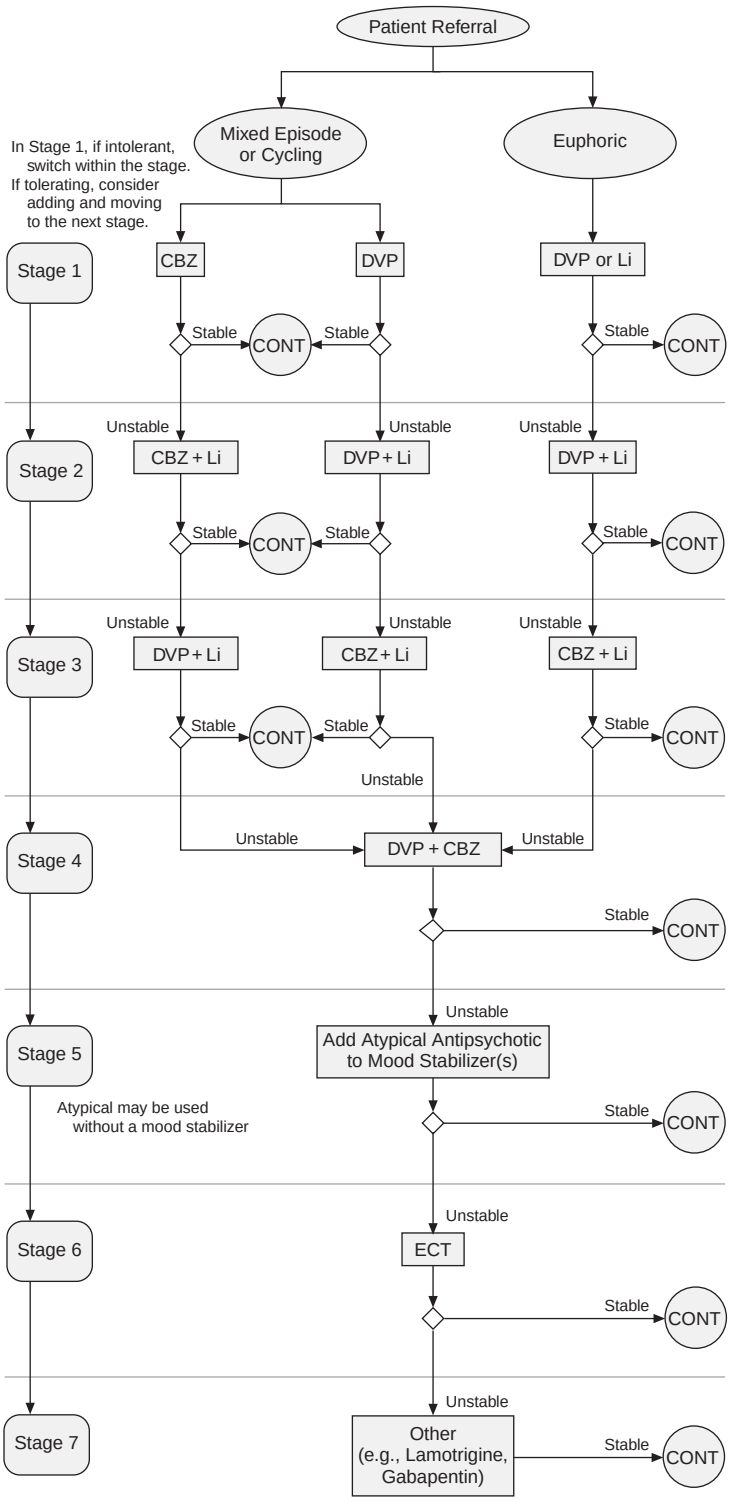
Within each ALGO clinic, all physicians utilized ALGO to treat BD. Other clinics were assigned to TAU and had the benefit of none of the elements of ALGO. A second comparison group, referred to as TAUinALGO, included clinics that used ALGO for major depressive disorder (MDD) or schizophrenia (SCZ) but not BD. This group was included to assess whether use of an algorithm (and supporting interventions) for a disorder other than BD would affect treatment of BD. The primary group for comparison was a priori planned to be ALGO versus TAU, with TAUinALGO available for secondary analyses. The current article describes the outcomes for patients in the primary comparison group: ALGO versus TAU.

Algorithm Intervention

The primary goal of ALGO was to optimize pharmacotherapy and to enhance clinical outcomes. Multiple tools were provided for the physicians and the treatment team to ensure maximal adherence to the algorithm. Each physician implemented ALGO in close collaboration with a clinical coordinator (an individual hired by the research project to work exclusively with patients and physicians in each ALGO clinic). The clinical coordinator met with patients immediately prior to their physician visit, completed symptom and side-effect ratings at each clinical visit to increase physician efficiency, maintained contact with the patient, provided information about implementation of ALGO to physicians, and administered the patient/family education program. The primary aim of pharmacotherapy was remission of symptoms and return to premorbid levels of psychosocial functioning. Physicians were reminded of these goals, and clinical coordinators were asked to prompt physicians when patient symptoms indicated incomplete response.

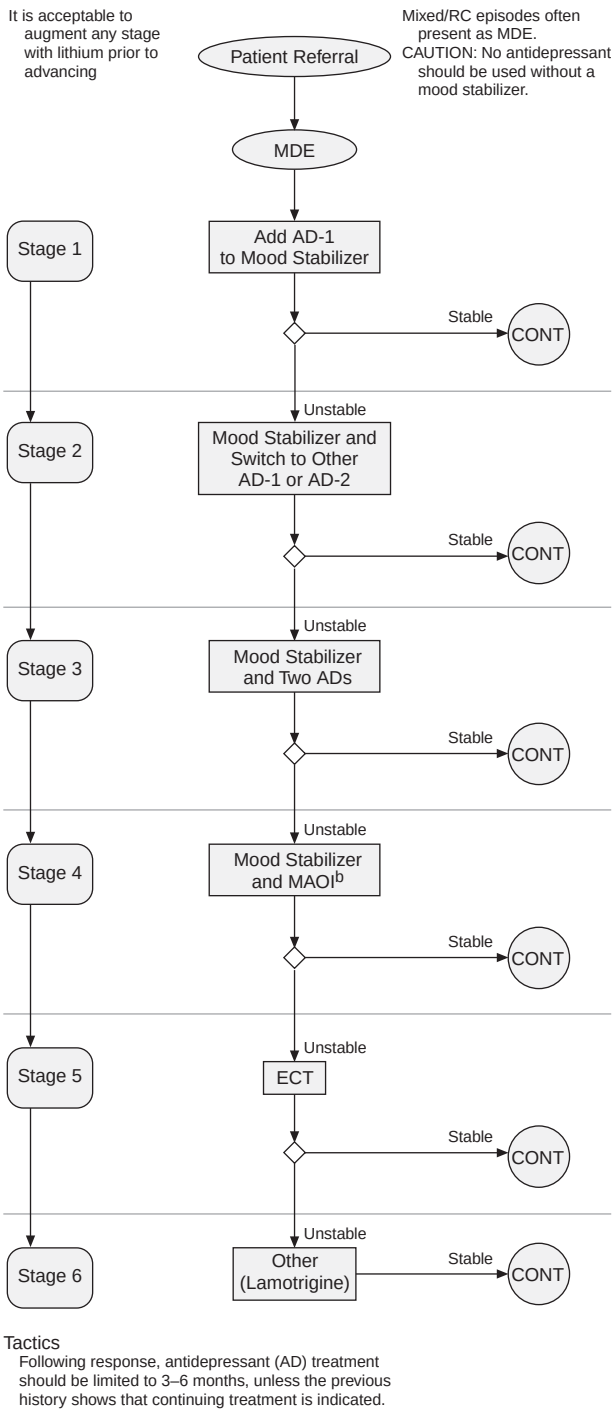
The TMAP Phase 3 algorithms for BD were developed by consensus and were generally derived from recommendations published by the Consensus Guideline Series[20,21] and the American Psychiatric Association,[22] incorporating past experiences with earlier phases of TMAP.[34] Consistent with all TMAP algorithms, the recommendations were arranged in linear, decision-tree formats, with specific critical decision criteria for duration of treatment, dosing, and adjunctive therapies described in the accompanying manual and support materials to assist the physician and clinical coordinator in implementing treatment. Separate algorithms for treatment of hypomania/

Figure 1. Algorithm for the Treatment of Bipolar Disorder (manic/hypomanic episode)[a]



[a]This material is in the public domain and can be reproduced without permission but with appropriate citation.
Abbreviations: CBZ = carbamazepine, CONT = continue, DVP = divalproex, ECT = electroconvulsive therapy, Li = lithium.

Figure 2. Algorithm for the Treatment of Bipolar Disorder (major depressive episode)[a]



[a]This material is in the public domain and can be reproduced without permission but with appropriate citation.
[b]Should not be used with carbamazepine, selective serotonin reuptake inhibitor (SSRI), or related compounds.
Abbreviations: AD-1 = bupropion SR or SSRI, AD-2 = venlafaxine or nefazodone, CONT = continue, ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, MDE = major depressive episode, RC = rapid cycling.

mania and major depressive episodes were developed (Figures 1 and 2). Each step in the 2 algorithms included multiple options based on available evidence and balancing issues of tolerability and safety. Earlier steps in the algorithm included options with the most evidence and the most favorable risk-benefit ratios. While physicians were encouraged to move linearly down the algorithms, it was understood that choices were made depending on patient history, physician judgment, and patient preference.

Physician implementation of the treatment recommendations was facilitated through multiple approaches. Both BD algorithms were accompanied by a detailed treatment manual. The monitoring of symptoms and side-effect burden was required at each clinic visit to optimize clinical decision making. The module director (T.S.), with assistance from other TMAP collaborators (E.S.B., M.L.C., E.B.D.), conducted regularly scheduled teleconferences to discuss individual cases and implementation and to provide recommendations based on the algorithms. Importantly, the ALGO intervention utilized a standardized Clinical Record Form, which was used to collect and structure information about medication adherence, side effects, current symptoms, and laboratory tests. This form was designed to facilitate decisions within the algorithm recommendations.

The treatment manual guided physicians through treatment decisions based upon algorithm stage, week of treatment, clinical response, side effects, and current medication serum levels (if applicable) using clinical decision trees. Response criteria were established to recommend either continuing on a stage, optimizing current medications, or changing stages or medications. These criteria were operationalized as the percentage of improvement on the 24-item Brief Psychiatric Rating Scale (BPRS-24)[37–39] relative to baseline: remission (75%–100%), high partial (50%–75%), low partial (25%–50%), and nonresponse (0%–25%). Decision points in the algorithm were geared to response (as defined above), duration of treatment, and tolerability considerations. The clinical decision trees provided visual cues that accounted for these factors and, if pertinent, serum levels of key medications.

A patient education package developed specifically for use in TMAP encouraged patient and family participation in treatment decisions as well as treatment adherence.[40] In the ALGO group, each patient and their family or significant others were offered participation in this step-wise education package, which was implemented by the clinical coordinator and provided information about the disease, prognosis, treatment options, side effects of medications, and self-management.

Subjects

Subjects were male and female outpatients, 18 years or older, with a DSM-IV clinical diagnosis of bipolar I disorder or schizoaffective disorder, bipolar type (referred to

collectively throughout as BD). Patients were enrolled into the ALGO or the TAU group based on their "home" clinic assignments. Patients entered the ALGO group if, in the judgment of their treating physician, they required a medication change or were starting a medication to treat symptoms of BD. Entrance into the TAU group initially utilized the same criteria. However, since medication changes were much less frequent in TAU, a patient was also recruited if his/her quarterly, routinely-administered BPRS-24 score was higher than the center median for each clinic's routine quarterly evaluation of all their patients. Once approached, another BPRS-24 interview was conducted, and patients with total BPRS-24 scores no more than 1 standard deviation (SD) below the already-enrolled ALGO patient average were asked to participate. This procedure ensured a minimal symptom severity for participation in TAU in the absence of a medication change.

Study exclusion criteria were minimal. Patients were excluded if they had SCZ, MDD, or other subtypes of schizoaffective disorder. Patients were also excluded if they required inpatient hospitalization for detoxification at the time of study entry or were receiving mental retardation services or treatment in an Assertive Community Treatment program.[41] Patients were excluded if they were not able to give informed consent to participate in the study evaluations.

Study Procedures

After obtaining written informed consent, participants provided demographic and medical history information at baseline and at outcome evaluations every 3 months for at least 12 months. The evaluator was not blinded to group assignment but was independent of the clinical management of participants.

Research Assessments

Enrollment for the study occurred over 13 months. Patients enrolling early could receive care for up to 24 months, with a minimum 12-month participation planned. As anticipated, the number of available assessments decreased substantially after the 12-month assessment. Therefore, only the first year of assessment is included in these results.

Clinical Outcomes

For patients in the BD module, the primary clinical outcome measure was the BPRS-24 total score, which assesses general psychiatric symptoms. Secondary symptom outcome measures included the mania and psychosis subscales of the Clinician-Administered Rating Scale for Mania (CARS-M)[42] and the 30-item Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C-30).[43] Other measures included health-related quality of life assessed by the Medical Outcomes Study 12-item Short Form Health Survey (SF-12)[44] and a patient global self-assessment of side-effect burden. For example, to assess side-effect burden, patients were asked the following question: "During the last month, have you had any side effects from your medication?" "If so, how much did these side effects bother you or interfere with your daily functioning?" If the patient reported, "no side effects" or "only mild side effects, not really significant," the patient was classified as having no significant side effects. Alternatively, patients were classified as having significant side effects if they responded, "side effects bothered me, but I could tolerate them," "side effects really bothered me, I either need to change my medication or take something for the side effects," or "side effects were so severe I had to be hospitalized."

Other measures were collected quarterly and included mental health and general medical service utilization via the 15-item Utilization and Cost Patient Questionnaire (UAC-PQ-15),[3] drug and alcohol use via the Michigan Alcoholism Screening Test (MAST)[45] and Drug Abuse Screening Test (DAST),[46] and a modified version of the Internal State Scale (ISS).[47,48] The Patient Perception of Benefits (PPB; Kashner, unpublished rating scale, 1996) was collected at baseline only. All medications taken for both psychiatric and medical conditions were noted throughout the study. These findings will be reported elsewhere. Evaluable patients included all patients completing baseline and at least 1 quarterly evaluation with the BPRS-24.

Statistical Analyses

Tests for differences between groups were based on 2-tailed tests with equal variance not assumed for continuous measures (based on Levene's test), chi-square for discrete values, and chi-square with continuity corrections for dichotomous measures.

As described by Rush et al.,[36] this issue, hierarchical linear models (HLMs)[49] were adapted to assess the impact of ALGO on patient outcomes based on a declining-effects analysis developed for this study by Kashner et al.[50,51]

Traditional HLM analyses are powered to detect growth in effect size over time. Initial examination of our data, however, indicated an initial superior effect for ALGO and, in some analyses, a tendency for TAU to catch up with ALGO over time (i.e., the declining effect). This declining effect over time after an initial effect may actually be expected for chronic diseases when the service intervention is expected to enhance the speed of recovery anticipated from traditional care. The more usual growth models have less power to detect initial effects that will eventually decline or remain constant over time.

Evaluation of the initial change in outcomes between baseline and the first 3-month assessment were computed separately for ALGO and for TAU. Following the initial

change, we calculated a growth rate in outcomes (change per quarter) during follow-up (3–12 months). An ALGO treatment effect was assessed by computing the difference in initial change (initial effect) and in growth rates (growth-rate effect) between ALGO and TAU. Growth-rate effects were used to compute whether initial effects increased, remained constant, or declined during follow-up. All estimates were adjusted to reflect baseline differences in patient outcomes (change scores) and baseline patient characteristics, including factors relating to need (baseline symptoms, age), enabling factors (family size, disposable income), predisposing factors (years of education, PPB total score), and other factors (gender and ethnicity). Hierarchical linear modeling analysis also allowed us to factor in time of entry into the study to adjust for possible effects due to this variable.

Specifically, time of observation since baseline was entered as a continuous variable in a time-specific (level I) and patient-specific (level II) HLM. Dependent variables were patient outcomes assessed at different time points and computed as change scores by subtracting each follow-up assessment by the respective value determined at baseline. For each treatment group (ALGO and TAU), the initial change during the first 3 months and growth rates were computed by the regression constant and coefficient to the time variable, respectively. To determine the impact of ALGO over TAU, initial and growth-rate effects are computed by a group-indicator and group-indicator × time interaction term. The group-indicator variable assumes the value of 1 for ALGO patients and 0 for TAU patients.

A logistic HLM was used to examine the impact on side-effect burden, a dichotomous variable. To adjust for regression to the mean, separate analyses were conducted for patients reporting (and not reporting) significant side effects at baseline.

Additional exploratory analyses were conducted to determine whether symptom severity at baseline affected initial and growth effects. These analyses were conducted to determine whether a particular subgroup of patients especially benefited from the ALGO intervention and to inform future studies in this area.

RESULTS

A total of 459 patients met study criteria for the BD module and gave informed consent. Of these, 14 did not complete baseline, 30 failed to report for any follow-up visit, and 6 had a follow-up visit that did not include the primary symptom measure (BPRS-24). The remaining 409 evaluable patients completed the BPRS-24 at baseline and at least 1 quarterly assessment, including 141 patients from 4 ALGO clinics, 126 patients from 7 clinics using no algorithms for any of the 3 disorders (TAU), and 142 patients from 4 clinics using an algorithm for medication treatment of SCZ or MDD but not for BD (TAUinALGO). The current article presents the clinical outcomes for the analytic sample, which was the a priori designated study and control groups, ALGO and TAU (total N = 267).

Subjects included 141 patients who attended 1 of 4 clinics (30%, 29%, 24%, and 17%, respectively) providing ALGO for BD and 126 patients who attended 1 of 7 clinics (32%, 15%, 13%, 12%, 11%, 9%, and 8%, respectively) in which no ALGO for any disorder was implemented (TAU). The mean age was similar in both groups (ALGO = 38 years; TAU = 40 years). Most patients were women (ALGO = 72%; TAU = 63%). The ALGO group contained significantly more African Americans (ALGO = 17%; TAU = 6%), shorter length of illness (ALGO = 11 years; TAU = 19), and higher reported disposable income (ALGO = $559/month; TAU = $339/month) than TAU. Education, marital status, employment, and other demographic characteristics are shown in Table 1.

Most patients (83%) were diagnosed with bipolar I disorder, but 17% were diagnosed with schizoaffective disorder, bipolar type. At study baseline (N = 267: ALGO = 141; TAU = 126), 69 patients (26%) were evaluated as manic, 17 of these (25%) with psychotic features. Seventy-one individuals (27%) were diagnosed as mixed, 15 of these (21%) with psychotic features. An additional 66 patients (25%) were described as depressed, and 17 of these patients (26%) experienced psychotic features. Finally, 61 patients (23%) did not have specifiers in their physician-assigned DSM-IV diagnosis. Evaluation of mood state at study entry was based on clinical evaluation.

The baseline BPRS-24 mean ± SD total score was lower, but not statistically different, for ALGO than for TAU patients (51.8 ± 14.4 versus 54.0 ± 12.4; ΔBPRS-24 = –2.17, $t = 1.32$, $df = 265$, $p < .19$). Therefore, regression to the mean would work against finding a favorable ALGO effect on outcome. This is further evidence that the analytic approach was conservative.

In general, covariates were not statistically significant predictors of change scores. Thus, potential biases introduced by these factors are expected to be small. However, BPRS-24 change scores tended to drop by an additional –0.55 points (SE = .05, $t = 11.56$, $df = 225$, $p < .001$) for each BPRS-24 point that baseline symptom scores were above mean values.

The study demonstrated substantial retention over time, with 267 (100%) participating at 3 months, 246 (92%) at 6 months, 229 (86%) at 9 months, and 216 (81%) at the 12-month assessment point. Retention was similar between the ALGO and TAU groups, with 77% of ALGO retained at 12 months compared with 81% of TAU.

The primary outcome measure was the BPRS-24. Both groups (ALGO and TAU) demonstrated significant initial decreases in symptoms at the 3-month assessment (initial

Table 1. Baseline Demographic Characteristics of ALGO Versus TAU for Patients in BD Module

Characteristic	ALGO (N = 141)	TAU (N = 126)	Statistic
Age, mean ± SD, y	38.3 ± 10.6	39.7 ± 10.0	t = 1.12, df = 262, p < .27
Age, y, %			χ^2 = 3.70, df = 5, p < .59[a]
≤ 19	2.1	1.6	
20–29	20.7	16.9	
30–39	28.6	29.0	
40–49	33.6	36.3	
50–59	11.4	15.3	
60–69	3.6	0.8	
Women, %	72.3	62.7	χ^2 = 2.41, df = 1, p < .12[a]
Ethnicity, %			χ^2 = 9.52, df = 3, p < .02[a]
African American	17.0	6.4	
Hispanic	24.1	30.4	
White	58.9	61.6	
Other	0	1.6	
High school graduate (or GED), %	77.9	80.5	χ^2 = 0.14, df = 1, p < .71[a]
Years in school, mean ± SD	12.2 ± 2.7	12.3 ± 3.3	t = 0.15, df = 259, p < .88
Marital status, %			χ^2 = 2.53, df = 4, p < .64[a]
Divorced	30.2	27.4	
Married	24.5	23.4	
Single (never married)	30.9	37.9	
Separated	12.2	8.1	
Widowed	2.2	3.2	
Employment, %			χ^2 = 0.13, df = 2, p < .94[a]
Full-time	12.3	13.0	
Part-time	14.5	13.0	
Unemployed	73.2	74.1	
Receiving financial assistance, %[b]	48.9	49.2	χ^2 = 0.00, df = 1, p < 1.0[a]
Receiving Medicaid, %	51.1	55.6	χ^2 = 0.37, df = 1, p < .54[a]
Family size, mean ± SD	1.9 ± 1.9	1.6 ± 1.7	t = 1.54, df = 262, p < .13
Living alone, %	23.4	28.0	χ^2 = 0.51, df = 1, p < .47[a]
Disposable monthly income, mean ± SD, $[c]	559.4 ± 707.3	338.8 ± 429.0	t = 2.94, df = 205, p < .004
Length of illness, mean ± SD, y	10.6 ± 11.2	19.3 ± 12.3	t = 6.02, df = 254, p < .00
Concurrent alcohol problems, %[d]	30.9	41.5	χ^2 = 2.70, df = 1, p < .10[a]
Concurrent drug problems, %[e]	7.9	13.0	χ^2 = 1.37, df = 1, p < .24[a]
Significant side effects, %[f]	48.9	42.1	χ^2 = 0.99, df = 1, p < .32[a]
Concurrent medical conditions, %			χ^2 = 1.22, df = 3, p < .75[a]
None	39.0	44.4	
1	29.8	24.6	
2	17.0	15.9	
3+	14.2	15.1	
PPB score, mean ± SD[g]	17.5 ± 5.7	20.8 ± 8.9	t = 3.54, df = 202, p < .00

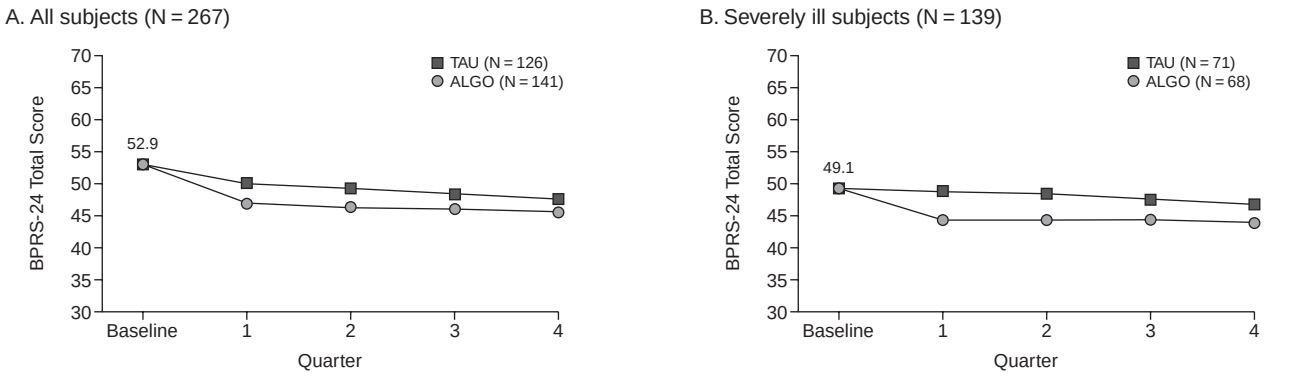
[a]2 × 2 using χ^2 with continuity correction.
[b]Includes food stamps.
[c]Total monthly income minus rent or mortgage payment.
[d]Scores of ≥ 5 on the Michigan Alcohol Screening Test indicate alcoholism.
[e]Scores > 5 on the Drug Abuse Screening Test indicate drug problems.
[f]Patient reported moderate to severe side effects from medication for month prior to baseline.
[g]A 10-item questionnaire ranging in score from 10 to 50, where 10 indicates patients strongly agree they will obtain improved functioning if they get the care they need, and 50 indicates patients strongly disagree that they will obtain improved functioning if they get the care they need.
Abbreviations: ALGO = algorithm-guided treatment, BD = patients with a history of mania, GED = general education development, PPB = Patient Perception of Benefits scale, TAU = treatment-as-usual.

Table 2. Baseline BPRS-24 Scores Adjusted Estimates of Initial Effect, Growth-Rate Effect, and Initial Effect × Growth-Rate Effect Differences Between ALGO and TAU Patients with BD[a]

	TAU (N = 126)				ALGO (N = 141)				Difference			
	γ	df	t	p	γ	df	t	p	γ	df	t	p
Initial effect	–2.65 ± 1.18	225	2.24	.03	–6.02 ± 0.92	225	6.53	< .001	–3.37 ± 1.54	972	2.19	.03
Growth-rate effect	–0.90 ± 0.32	972	2.79	.006	–0.44 ± 0.27	972	1.64	.10	0.46 ± 0.42	972	1.11	.27

[a]Coefficients represented as mean value ± SE. Adjusted for mean values by group (all, very severe, severe, and mild/moderate psychiatric symptoms) with respect to baseline BPRS-24 score, age (years), family size, disposable income, years of education, PPB total score, gender, and ethnicity (African American and Hispanic). For all patients, baseline BPRS-24 values were 51.83 ± 14.38 (ALGO) and 54.00 ± 12.39 (TAU) for a mean difference of –2.17 ± 1.64 (t = 1.32, df = 264, p = .19, equal variances not assumed, 2-tailed test) suggesting a negligible regression to the mean bias that works against finding an ALGO effect of lower BPRS-24 follow-up scores.
Abbreviations: ALGO = algorithm-guided treatment, BD = patients with a history of mania, BPRS-24 = 24-item Brief Psychiatric Rating Scale, PPB = Patient Perception of Benefits scale, TAU = treatment-as-usual.

Figure 3. Symptom Decrease According to Adjusted Mean BPRS-24 Scores



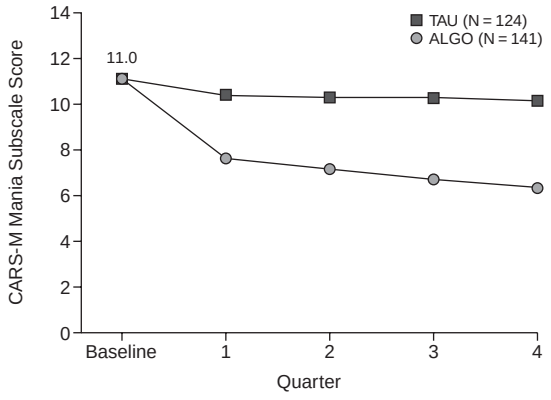
Abbreviations: ALGO = algorithm-guided treatment, BPRS-24 = 24-item Brief Psychiatric Rating Scale, TAU = treatment-as-usual.

Table 3. Baseline CARS-M Mania Subscale Score Adjusted Estimates of Initial Effect, Growth-Rate Effect, and Initial Effect × Growth-Rate Effect Differences Between ALGO and TAU Patients with BD[a]

	TAU (N = 126)				ALGO (N = 141)				Difference			
	γ	df	t	p	γ	df	t	p	γ	df	t	p
Initial effect	–0.61 ± 0.76	222	0.80	.42	–3.45 ± 0.65	222	5.31	< .001	–2.84 ± 1.05	963	2.71	.007
Growth-rate effect	–0.05 ± 0.20	963	0.27	.78	–0.36 ± 0.14	963	2.49	.013	–0.30 ± 0.24	963	1.24	.21

[a]Coefficients represented as mean value ± SE. Adjusted for mean values by group (all, high, medium, and low mania symptoms) with respect to baseline BPRS-24 score, age (years), family size, disposable income, years of education, PPB total score, gender, and ethnicity (African American and Hispanic). For all patients, baseline CARS-M mania subscale values were 11.48 ± 7.92 (ALGO) and 10.45 ± 6.97 (TAU) for a mean difference of 1.03 ± 0.92 (t = 1.12, df = 260, p = .26, equal variances not assumed, 2-tailed test) suggesting a negligible regression to the mean bias that works favoring finding an ALGO effect of lower CARS-M mania subscale follow-up scores.
Abbreviations: ALGO = algorithm-guided treatment, BD = patients with a history of mania, BPRS-24 = 24-item Brief Psychiatric Rating Scale, CARS-M = Clinician-Administered Rating Scale for Mania, PPB = Patient Perception of Benefits scale, TAU = treatment-as-usual.

Figure 4. Adjusted Mean CARS-M Mania Subscale Scores for All Subjects



Abbreviations: ALGO = algorithm-guided treatment, CARS-M = Clinician-Administered Rating Scale for Mania, TAU = treatment-as-usual.

effect; Table 2). The initial improvement was significantly greater for ALGO than for TAU (p = .03). Over the course of months 3 through 12, TAU patients significantly improved by 0.9 BPRS-24 points per quarter compared with their ALGO counterparts' improvement of 0.4 points per quarter (p = .27), although the difference in growth rate was not statistically significant.

Exploratory analyses divided the sample into very severely ill (BPRS-24 score ≥ 60), severely ill (BPRS-24 score = 40–59), and moderately ill (BPRS-24 score ≤ 39) subgroups. For the very severely ill group (mean BPRS-24 score = 69), both ALGO and TAU experienced significant initial decreases and subsequent improvement over time. For the severely ill group (mean BPRS-24 score = 49), ALGO produced a significant initial effect that declined further, although not significantly, over the remaining 8 months of observation (Figure 3). There were no between-group differences seen in the moderately ill subgroup (mean BPRS-24 score = 34).

Symptoms of hypomania and mania as measured by the CARS-M mania subscale declined significantly more over the first quarter of treatment with ALGO as compared with TAU (Table 3). With a mean baseline score of 11 for both groups, CARS-M mania subscale scores in the ALGO group declined 3.5 points in the first quarter, while those in the TAU group declined only 0.6 points. ALGO scores continued to decline over time, although the ALGO growth rate was not statistically different from that observed in TAU (p = .21; Figure 4). ALGO patients also had a larger initial drop in psychotic symptoms, measured via the psychosis subscale of the CARS-M, of 0.82 points (p < .001) after an increase of 0.23 points in TAU patients (p = .47; Table 4). Further improvement in symptoms

Table 4. Baseline CARS-M Psychosis Subscale Score Adjusted Estimates of Initial Effect, Growth-Rate Effect, and Initial Effect × Growth-Rate Effect Differences Between ALGO and TAU Patients with BD[a]

	TAU (N = 126)				ALGO (N = 141)				Difference			
	γ	df	t	p	γ	df	t	p	γ	df	t	p
Initial effect	0.23 ± 0.32	222	0.73	.47	–0.82 ± 0.26	222	3.21	< .001	–1.05 ± 0.43	962	2.46	.014
Growth-rate effect	–0.23 ± 0.09	962	2.73	.007	0.03 ± 0.07	962	0.47	.64	0.26 ± 0.11	962	2.46	.014

[a]Coefficients represented as mean value ± SE. Adjusted for mean values by group (all, high, medium, and low psychosis symptoms) with respect to baseline BPRS-24 score, age (years), family size, disposable income, years of education, PPB total score, gender, and ethnicity (African American and Hispanic). For all patients, baseline CARS-M psychosis subscale values were 3.46 ± 3.43 (ALGO) and 4.17 ± 3.63 (TAU) for a mean difference of 0.70 ± 0.43 (t = 1.62, df = 263, p = .11, equal variances assumed, 2-tailed test) suggesting a negligible regression to the mean bias that works against finding an ALGO effect of lower CARS-M psychosis subscale follow-up scores.

Abbreviations: ALGO = algorithm-guided treatment, BD = patients with a history of mania, BPRS-24 = 24-item Brief Psychiatric Rating Scale, CARS-M = Clinician-Administered Rating Scale for Mania, PPB = Patient Perception of Benefits scale, TAU = treatment-as-usual.

Table 5. Baseline IDS-C-30 Score Adjusted Estimates of Initial Effect, Growth-Rate Effect, and Initial Effect × Growth-Rate Effect Differences Between ALGO and TAU Patients with BD[a]

	TAU (N = 126)				ALGO (N = 141)				Difference			
	γ	df	t	p	γ	df	t	p	γ	df	t	p
Initial effect	–1.98 ± 1.18	222	1.67	.09	–4.25 ± 1.15	222	3.69	< .001	–2.27 ± 1.73	964	1.31	.19
Growth-rate effect	–0.34 ± 0.39	964	0.87	.39	–0.22 ± 0.26	964	0.88	.38	0.11 ± 0.46	964	0.24	.81

[a]Coefficients represented as mean value ± SE. Adjusted for mean values by group (all, high, medium, and low clinical depressive symptoms) with respect to baseline BPRS-24 score, age (years), family size, disposable income, years of education, PPB total score, gender, and ethnicity (African American and Hispanic). For all patients, baseline IDS-C-30 values were 30.35 ± 14.51 (ALGO) and 31.55 ± 14.53 (TAU) for a mean difference of –1.20 ± 1.80 (t = 0.67, df = 261, p = .51, equal variances assumed, 2-tailed test) suggesting a negligible regression to the mean bias that works against finding an ALGO effect of lower IDS-C-30 follow-up scores.

Abbreviations: ALGO = algorithm-guided treatment, BD = patients with a history of mania, BPRS-24 = 24-item Brief Psychiatric Rating Scale, IDS-C-30 = 30-item Inventory of Depressive Symptomatology, Clinician-Rated, PPB = Patient Perception of Benefits scale, TAU = treatment-as-usual.

for ALGO and TAU was observed, with TAU showing "catch-up" over the remaining 9 months of assessment.

Overall, initial changes in depressive symptoms, as measured by the IDS-C-30 (Table 5), did not differ significantly between the ALGO and TAU groups. Analyses of subgroups defined by baseline symptom severity revealed a significant initial effect for the high depression subgroup (IDS-C-30 score ≥ 46). Depressive symptom scores dropped an average of 16.5 points ($p < .001$) for the ALGO group over the first quarter, which was significantly greater than the initial depressive symptom reduction in TAU (–6.00 ± 2.79; $p < .039$). However, continued decreases in TAU depressive symptom scores over the next 3 quarters relative to the ALGO group suggest that there was a "catch-up" effect in the TAU group.

No differences were observed between ALGO and TAU on SF-12 Mental Health Summary (MHS) or Physical Health Summary (PHS) scores. For those patients with the highest mental functioning at baseline (SF-12 MHS score ≥ 50), there was a significant initial reduction in mental functioning among TAU patients (–9.4 ± 2.1, df = 19, t = 4.45, $p < .001$) but not among ALGO patients (–1.5 ± 2.7, df = 19, t = 0.53, $p < .60$), resulting in a significant ALGO initial effect (ΔSF-12 MHS = 7.9 ± 3.8, df = 119, t = 2.08, $p < .037$).

Safety and Tolerability

ALGO patients with significant side-effect burden at baseline (N = 68) reported a numerically lower burden from medication side effects at the end of 3 months than did their TAU counterparts (N = 53), though the difference was not statistically significant (odds ratio [OR] = 0.58, 95% confidence interval [CI] = 0.27 to 1.26, t = 1.38, df = 406, $p < .17$). During months 3 through 12, TAU patients demonstrated "catch-up" to their ALGO counterparts (OR = 1.44, 95% CI = 1.09 to 1.90, t = 2.55, df = 406, $p < .011$), as fewer TAU patients reported significant side effects with time (OR = 0.73/quarter, 95% CI = 0.59 to 0.90, t = 2.89, df = 406, $p < .004$) while the degree of side effects reported by ALGO patients remained unchanged (OR = 1.05/quarter, 95% CI = 0.88 to 1.26, t = 0.56, df = 406, $p < .58$). No statistically significant difference between ALGO and TAU was found either initially after the first quarter (OR = 1.58, 95% CI = 0.78 to 3.17, t = 1.27, df = 523, $p < .21$) or in growth rates during follow-up (OR = 0.84/quarter, 95% CI = 0.68 to 1.03, t = 1.67, df = 523, $p < .095$) for patients who did not report significant side-effect burden at baseline.

DISCUSSION

This is the first study to assess the effectiveness of treatment algorithms for BD in the public mental health sector. On the primary outcome measure (BPRS-24), a general measure of the severity of psychiatric symptoms, ALGO produced a larger initial decrease in symptoms during the first 3 months of treatment. Changes in symptoms over the next 3 quarters (months 3–12) revealed similar improvement for patients in both ALGO and TAU, particularly in patients who were classified at baseline as

"very severely ill." In very severely ill patients, catch-up by TAU was seen. It is possible that for patients who are very severely ill, treatment of any type results in some symptom reduction. For patients who were "severely ill" at baseline, ALGO appeared to provide an initial significant advantage compared with the TAU group, which continued over the subsequent 9 months. Thus, for those patients presenting with moderate psychiatric severity, treatment with ALGO appeared to provide an advantage that was sustained over time. The increased visits and constant reminders of potential interventions to optimize pharmacotherapy may have facilitated treatment gains that otherwise would not have been realized.

Symptoms of mania and psychosis (measured by relevant subscales of the CARS-M) declined significantly more in the ALGO group than in the TAU group over the first 3 months of treatment. Between-group differences in hypomania/mania as measured by the mania subscale of the CARS-M were sustained over the 12-month study, indicating an overall significant advantage for the ALGO group. This impact may be related to ready access to the newer antimanic agents such as the atypical antipsychotics or possibly other factors, including access to care through the ALGO clinical coordinators. While there was an initial between-group difference on the psychosis subscale of the CARS-M, there was overall catch-up over 12 months with minimal between-group differences by 12 months. This may reflect the typical treatment response time within this public mental health setting coupled with the relative efficacy of both the typical and atypical antipsychotics to decrease the type of positive symptoms assessed by the psychosis subscale of the CARS-M.

There were no differences observed in the change in depressive symptoms between the ALGO and TAU groups as a whole. For patients with the highest levels of initial depression, however, a significant initial effect for ALGO was found, with a large decrease in depressive symptom scores at the 3-month assessment. The TAU group was able to "catch up" to the depressive symptom reduction over the following 9 months of treatment. The difficulty of treating depressive episodes in patients with bipolar disorder is often recognized.[52,53]

Recent studies, have increased awareness that bipolar disorder is associated with considerable dysfunction, despite improvement of symptoms.[52,54–56] In this severely and persistently ill group of patients, the initial gains indicating significant effects in the first 3 months of treatment with the ALGO package are of significant note. While a degree of declining effects was observed in that improvement did not continue at the same rate, initial gains were sustained. In the course of this lifelong illness, initial, sustained gains may represent significantly improved quality of life and overall decreased symptoms.

The difficulty of completing maintenance studies and, in particular, 12-month or longer trials in patients with bipolar disorder has recently been addressed.[57,58] Relatively few 12-month or longer studies have been completed in the last 10 years and particularly with such a severely impaired group of patients.[7,59] Research evaluating response in severely ill patients with significant comorbidity is sorely needed.[60] The findings from this study and the extensive database collected during its course will provide an opportunity to enhance our understanding of course of illness, treatment response, and important covariates of a particularly ill group of patients with a history of mania.

While we do not know which specific intervention, medication, or combination within the algorithm package was critical to showing between-group differences, it is noteworthy that in this first algorithm implementation study, significant between-group findings were seen in the primary outcome (BPRS-24) and some secondary symptom measures (e.g., CARS-M). In other secondary assessments, including the IDS-C-30, SF-12, and side-effect burden, a numerical initial effect was seen in favor of ALGO.

On the SF-12 MHS and PHS, no significant differences were noted between ALGO and TAU. However, for patients with higher (i.e., better) levels of initial mental functioning, TAU patients experienced a worsening in mental functioning over the first quarter of assessment relative to their ALGO counterparts. While we are cautious in assessing the relevance of this finding, as the comparison included only 33 patients, one factor contributing to between-group differences may have been access to newer medications for the ALGO group. In terms of side effects, no significant effects were noted between groups. As observed in other studies,[35] no significant increases in somatic complaints were observed when medications were added or potentially stronger medications were substituted.

TMAP is remarkable for the inclusion of a group of severely and persistently ill patients not usually observed in research settings. This group presented with significant length of illness, poor psychosocial functioning, heavy reliance on public assistance, substantial concurrent medical comorbidities, and ongoing symptoms with a history of prior treatments that were not fully successful. In addition, the sample was ethnically diverse and reasonably representative of the population served in the public mental health system of Texas. Thirty-six percent had concurrent alcohol problems (according to the MAST), and 10% reported drug problems (via the DAST) in addition to serious psychiatric illness. Additionally, as seen in baseline scores on the BPRS-24, CARS-M, and IDS-C-30, the group presented with significant baseline psychiatric severity (Tables 1–3). It is noteworthy that, as compared with randomized controlled trials, this study population represented significant heterogeneity. Patients entered the study in different phases of the illness (mixed, manic,

depressed) and with various degrees of symptom severity, substantial psychiatric and medical comorbidity, and significant psychosocial impairment. These findings highlight the utility of services research, where patient populations more closely resemble the diversity of clinical practice.[8,61] Given this heterogeneity, it is perhaps more striking that results indicated some degree of both initial and sustained benefit from the ALGO package.

The apparent benefits of ALGO are noteworthy considering that participation in the research was voluntary, adherence to the algorithm varied among physicians and clinics, and that active treatments were compared. Physicians deviated from the algorithm recommendations at times, despite surveillance and feedback from the study management team and a clinical coordinator located in their clinic.[62–65] It is possible that adherence could be improved by more immediate audit and feedback or reminders in the context of the physician visit of the appropriate step in algorithm implementation given the stage of treatment, consideration of objectively measured symptoms, and report of side effects.[63] Further examinations of the impact of physician adherence on clinical outcomes are planned as well as of details regarding the effectiveness of specific medications and medication combinations.

Limitations of the present study include the lack of randomization, as matched clinics within the Texas public mental health system were assigned to treatment condition (ALGO or TAU). Another potential criticism is the decision not to use physician or patient as the unit of randomization. Slightly different inclusion criteria were used for ALGO and TAU, which may have affected outcome. However, the statistical analyses were chosen to correct for many of the factors that could contribute to spurious group differences. In particular, the HLM analysis allows designs that utilize ongoing enrollment (i.e., different times of study entry) that could substantially modify findings and includes adjustments for variables that could amplify between-group differences, such as ethnicity. Outcome assessment personnel, while not blinded to treatment assignment, had no role in the clinical management of study patients. While this is a limitation of the study, the lack of a uniform benefit for the ALGO group makes it less likely that there was a systematic assessment bias in favor of ALGO.

In many instances, TAU patients caught up to the initial benefits observed in ALGO patients. It is possible that clinical effects observed may have been due to the episodic nature of bipolar disorder, although the repeated assessments over extended time periods minimize this possibility. Future analyses will examine the extent to which care for TAU patients differed from care for ALGO patients. There is some evidence that ALGO patients and physicians had more ready access to newer medications. However, it is possible that TAU physicians were able to prescribe newer medications more than anticipated, that they were reading and following treatment recommendations of other experts or published guidelines, and that pharmacological care did not differ substantially across the 2 groups. Nevertheless, the ALGO package included multiple other therapeutic modalities, including patient and family education and more frequent contact with clinical staff, thus representing a disease management model of care.

The study was limited somewhat by structural issues endemic to the public mental health system in which it was conducted. For example, large patient-physician ratios limited the ability to schedule visits at timely intervals in some locations and excessive physician turnover (over 200% in one ALGO clinic over the study duration) clearly impacted continuity of care. This type of issue is common to many mental health settings. The importance of finding an initial and sustained benefit for the group receiving treatment with the ALGO package is highlighted when the overstressed and underresourced system the study was conducted in is considered.

Finally, it should be emphasized that these outcomes relate specifically to the implementation of the TMAP Phase 3 ALGO package for BD patients. The package included medication algorithms, a comprehensive patient and family education program, additional individual staff time and attention, increased visits, uniform documentation, and access to new generation medications not readily available in all locations. At this time, the relative contribution of different elements of the "disease management package" to the obtained results has not been evaluated.

Subsequent analyses will address additional specifics regarding the role of physician adherence and the effectiveness of certain medications and medication combinations for this patient population. In particular, the impact of ethnicity will be evaluated across clinical outcome domains. Additional analyses on quality of life and economic impact of ALGO versus TAU are planned. These later analyses are clearly pertinent to evaluating the effects of interventions on overall service utilization for public payer systems. These analyses will examine the costs associated with implementing the ALGO, including potential cost offsets, such as hospitalization and contacts with the criminal justice system.

Drug names: bupropion SR (Wellbutrin SR), carbamazepine (Carbatrol, Tegretol, and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), nefazodone (Serzone), venlafaxine (Effexor).

Direct funding/support: This research was supported by National Institute of Mental Health (NIMH) Grant MH-53799; the Robert Wood Johnson Foundation; the Meadows Foundation; the Lightner-Sams Foundation; the Nanny Hogan Boyd Charitable Trust; the Texas Department of Mental Health and Mental Retardation; the Center for Mental Health Services; the Department of Veterans Affairs; Health Services Research and Development Research Career Scientist Award (RCS92-403) (Dr. Kashner); the Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical

Science (Dr. Rush); the United States Pharmacopoeia Convention, Inc.; Mental Health Connections (a partnership between Dallas County Mental Health and Mental Retardation [MHMR] and the Department of Psychiatry of the University of Texas Southwestern Medical Center, which receives funding from the Texas State Legislature and the Dallas County Hospital District); the University of Texas at Austin College of Pharmacy; and the Southwestern Drug Corporation Centennial Fellowship in Pharmacy (Dr. Crismon). The following pharmaceutical companies provided unrestricted educational grants: Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, and WyethAyerst.

Financial disclosures: Dr. Suppes has served as a consultant or on the advisory board for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, and Pharmaceutical Research Institute; and has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, National Institute of Mental Health, Novartis, Robert Wood Johnson Foundation, and Stanley Medical Research Institute. Dr. Rush has served as a consultant for Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, and Stanley Medical Research Institute; has received grant/research support from Cyberonics, Robert Wood Johnson Foundation, National Institute of Mental Health, and Stanley Medical Research Institute; and has served on the speakers bureau for Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, and Wyeth. Dr. Crismon has served as a consultant for Merck Medco Managed Care, Radiant Research, Magellan Behavioral Care, and Bristol-Myers Squibb; has received grant/research support from AstraZeneca, Eli Lilly, Forest, Janssen, and Pfizer; has served on the advisory board for Janssen, Pharmacia, and Pfizer; has served on the speakers bureau for or been sponsored for lectures or development of CME materials by AstraZeneca, Eli Lilly, Forest, Janssen, Pharmacia, and Pfizer; and is a partner of Texas Research Associates. Dr. Kashner is an employee of University of Texas Southwestern Medical Center, VA Medical Center, and the Department of Veterans Affairs. Dr. Brown has received grant/research support from Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Forest, National Institute of Mental Health, and Stanley Medical Research Institute; and has received honoraria from AstraZeneca. Dr. Trivedi has received grant/research support from Abbott, Akzo Nobel (Organon), Bayer, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, National Institute of Mental Health, Mead Johnson, Parke-Davis, Pfizer, Pharmacia, Solvay, and Wyeth; and has served on the speakers bureau for Bristol-Myers Squibb, Eli Lilly, Forest, Janssen, Organon (Akzo Nobel), Pharmacia, Solvay, and Wyeth. Dr. Miller has served as a consultant for Janssen; has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer; has served on the speakers/advisory board for Abbott, Bristol-Myers Squibb, Astra-Zeneca, and Pfizer; and is a major stock shareholder of Pfizer and Wyeth. Dr. Altshuler has received grant/research support from Eli Lilly and Janssen.

Acknowledgments: The authors deeply appreciate the consultations provided by Barbara Burns, Ph.D.; Robert Drake, M.D.; Susan Essock, Ph.D.; William Hargreaves, Ph.D.; Teh-wei Hu, Ph.D.; Anthony Lehman, M.D.; and Greg Teague, Ph.D., without whose expertise this study could not have been accomplished.

We also thank the National and Texas Alliance for the Mentally Ill, the National and Texas Depressive and Manic Depressive Association, Mental Health Association in Texas, and Mental Health Consumers for providing patient and family educational materials. We appreciate greatly the assistance of Gus Sicard, Ph.D., for his translation of the educational, clinical, and research evaluation materials into Spanish.

We gratefully acknowledge Karla Starkweather (TMAP Communications Director, Texas Department of Mental Health and Mental Retardation, Austin) for her invaluable assistance in the conduct of this study. Most importantly, we wish to express our gratitude to the personnel at each Community Mental Health Center for allowing us to conduct this research with their staff and patients, including Andrews Center, Tyler, Tex.; Center for Health Care Services, San Antonio, Tex.; Life Management Center, El Paso, Tex.; Lubbock Regional MHMR Center, Lubbock, Tex.; MHMRA of Harris County, Houston, Tex.; Tri-County MHMR Services, Conroe, Tex.; and Tropical Texas MHMR Services, Edinburgh, Harlingen, and Brownsville.

We appreciate the secretarial support of FastWord, Inc. (Dallas) and David Savage, and we thank Andrew Sedillo, M.D., for establishing the TMAP Web site (http://www.mhmr.state.tx.us/CentralOffice/MedicalDirector/tmap.html). We would also like to thank the Assistant Module Directors: E. Sherwood Brown, M.D., Ph.D.; John Chiles, M.D.; and Teresa Pigott, M.D., and the Algorithm Management Team Coordinators: Judith Chiles, B.S.N., and Tracie Key, B.S.N., R.N.

REFERENCES

1. Regier DA, Myers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984;41:934–941
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Kashner TM, Suppes T, Rush AJ, et al. Measuring use of outpatient care among mentally ill individuals: a comparison of self-reports and provider records. Eval Program Plann 1999;22:31–39
4. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York: Oxford University Press; 1990
5. Coryell W, Scheftner W, Keller M, et al. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993;150:720–727
6. Gitlin MJ, Swendsen J, Heller TL, et al. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640
7. Suppes T, Webb A, Paul B, et al. Clinical outcome in a randomized one-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry 1999;156:1164–1169
8. Suppes T, Leverich GS, Keck PE Jr, et al. The Stanley Foundation Bipolar Treatment Outcome Network II: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–59
9. Harrow M, Goldberg JF, Grossman LS, et al. Outcome in manic disorders: a naturalistic follow-up study. Arch Gen Psychiatry 1990;47:665–671
10. Page C, Benaim S, Lappin F. A long-term retrospective follow-up study of patients treated with prophylactic lithium carbonate. Br J Psychiatry 1987;150:175–179
11. Maj M, Pirozzi R, Kemali D. Long-term outcome of lithium prophylaxis in patients initially classified as complete responders. Psychopharmacology (Berl) 1989;98:535–538
12. Peselow ED, Fieve RR, Difiglia C, et al. Lithium prophylaxis of bipolar illness: the value of combination treatment. Br J Psychiatry 1994;164:208–214
13. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness: efficacy, effectiveness and efficiency. Br J Psychiatry 1994;164:741–746
14. Markar HR, Mander AJ. Efficacy of lithium prophylaxis in clinical practice. Br J Psychiatry 1989;155:496–500
15. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997;58:470–478
16. Müller-Oerlinghausen B, Retzow A, Henn FA, et al. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. J Clin Psychopharmacol 2000;20:195–203
17. Sachs GS. Safety and efficacy of risperidone vs placebo as add-on therapy to mood stabilizers in the treatment of the manic phase of bipolar disorder. Presented at the 153rd annual meeting of the American Psychiatric Association; May 17, 2000; Chicago, Ill
18. Tohen M, Chengappa KNR, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002;59:62–69
19. Bauer MS, Callahan AM, Jampala C, et al. Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs. J Clin Psychiatry 1999;60:9–21
20. Expert Consensus Guideline Series: Treatment of Bipolar Disorder.

J Clin Psychiatry 1996;57(suppl 12A):1–89
21. Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000;Apr(spec. no.):1–104
22. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder. Am J Psychiatry 1994;151(suppl 12):1–36
23. Kusumakar V, Yatham LN, Haslam DRS, et al. Treatment of mania, mixed state, and rapid cycling. Can J Psychiatry 1997;42(suppl 2): 79S–86S
24. Yatham LN, Kusumakar V, Parikh SV, et al. Bipolar depression: Treatment options. Can J Psychiatry 1997;42(suppl 2):87S–91S
25. Jobson KO, Potter WZ. International Psychopharmacology Algorithm Project Report [introduction]. Psychopharmacol Bull 1995;31:457–459
26. Suppes T, Calabrese JR, Mitchell PB, et al. Algorithms for the treatment of bipolar manic-depressive illness. Psychopharmacol Bull 1995;31: 469–474
27. Goodwin GM, Bourgeois ML, Conti L, et al. Treatment of bipolar depressive mood disorders: algorithms for pharmacotherapy. Int J Psychiatry in Clin Pract 1997;1:S9–S12
28. Dennehy EB, Suppes T. Medication algorithms for bipolar disorder. J Pract Psychiatry Behav Health 1999;5:142–152
29. Bauer MS, Williford WO, Dawson EE, et al. Principles of effectiveness trials and their implementation in VA Cooperative Study #430: "Reducing the efficacy-effectiveness gap in bipolar disorder." J Affect Disord 2001;67:61–78
30. Gilbert DA, Altshuler KZ, Rago WV, et al. Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms. J Clin Psychiatry 1998;59:345–351
31. Crismon ML, Trivedi M, Pigott TA, et al, and the Texas Conference Panel on Medication Treatment of Major Depressive Disorder. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. J Clin Psychiatry 1999;60:142–156
32. Rush AJ, Rago WV, Crismon ML, et al. Medication treatment for the severely and persistently mentally ill: The Texas Medication Algorithm Project. J Clin Psychiatry 1999;60:284–291
33. Miller AL, Chiles JA, Chiles JK, et al. The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms. J Clin Psychiatry 1999;60:649–657
34. Suppes T, Swann AC, Dennehy EB, et al. Texas Medication Algorithm Project: development and feasibility testing of a treatment algorithm for patients with bipolar disorder. J Clin Psychiatry 2001;62:439–447
35. Suppes T, Rush AJ, Kraemer HC, et al. Treatment algorithm use to optimize management of symptomatic patients with a history of mania. J Clin Psychiatry 1998;59:89–96
36. Rush AJ, Crismon ML, Kashner TM, et al, for the TMAP Research Group. Texas Medication Algorithm Project, Phase 3 (TMAP-3): rationale and study design. J Clin Psychiatry 2003;64:357–369
37. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling [introduction]. Psychopharmacol Bull 1988;24:97–99
38. Ventura J, Green MF, Shaner A, et al. Training and quality assurance with the Brief Psychiatric Rating Scale: "the drift busters." Int J Methods Psychiatr Res 1993;3:227–244
39. Ventura J, Nuechterlein KH, Subotnik K, et al. Symptom dimensions in recent-onset schizophrenia: the 24-item expanded BPRS [abstract]. Schizophr Res 1995;15:22
40. Toprac MG, Rush AJ, Conner TM, et al. The Texas Medication Algorithm Project Patient and Family Education Program: a consumer-guided initiative. J Clin Psychiatry 2000;61:477–486
41. Stein LI, Test MA. Alternative to mental hospital treatment, 1: conceptual model, treatment program, and clinical evaluation. Arch Gen Psychiatry 1980;37:392–397
42. Altman E, Hedeker D, Janicak P, et al. The Clinician-Administered Rating Scale for Mania (CARS-M): development, reliability, and validity. Biol Psychiatry 1994;36:124–134
43. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26:477–486
44. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey (SF-12): construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233
45. Selzer MJ. The Michigan Alcoholism Screening Test: the quest for a new diagnostic instrument. Am J Psychiatry 1971;127:89–95
46. Skinner HA. The Drug Abuse Screening Test. Addict Behav 1982;7: 353–371
47. Bauer MS, Crits-Christoph P, Ball WA, et al. Independent assessment of manic and depressive symptoms by self-rating: scale characteristics and implications for the study of mania. Arch Gen Psychiatry 1991;48: 807–812
48. Bauer MS, Vojta C, Kinosian B, et al. The Internal State Scale: replication of its discriminating abilities in a multisite, public sector sample. Bipolar Disord 2000;2:340–346
49. Bryk AS, Raudenbush SW. Hierarchical Linear Models: Applications and Data Analysis Methods. Advanced Quantitative Techniques in the Social Sciences, vol 1. Newbury Park, Calif: SAGE Publications; 1992
50. Kashner TM, Carmody TJ, Suppes T, et al. Catching up on health outcomes: the Texas Medication Algorithm Project. HSR: Health Serv Res 2003;28:311–331
51. Kashner TM, Rosenheck R, Campinell AB, et al. Impact of work therapy on health status among homeless, substance dependent veterans: a randomized controlled trial. Arch Gen Psychiatry 2002;59:938–944
52. Coryell W, Turvey C, Endicott J, et al. Bipolar I affective disorder: predictors of outcome after 15 years. J Affect Disord 1988;50:109–116
53. Keller MB, Lavori PW, Coryell W, et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. JAMA 1986;255:3138–3142
54. Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry 2000;157:220–228
55. Keck PE Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry 1998;155:646–652
56. Zarate CA Jr, Tohen M, Land M, et al. Functional impairment and cognition in bipolar disorder. Psychiatr Q 2000;71:309–329
57. Bowden CL, Swann AC, Calabrese JR, et al. Maintenance clinical trials in bipolar disorder: design implications of the divalproex-lithium-placebo study. Psychopharmacol Bull 1997;33:693–699
58. Prien RF, Rush AJ. National Institute of Mental Health workshop report on the treatment of bipolar disorder. Biol Psychiatry 1996;40:215–220
59. Bowden CL, Calabrese JR, McElroy SL, et al, for the Divalproex Maintenance Study Group. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57:481–489
60. National Institute of Mental Health. Bridging Science and Service: A Report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup. Rockville, Md: National Institute of Health; 1999. NIH publication no. 99-4353
61. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994;31:281–294
62. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? a framework for improvement. JAMA 1999;282:1458–1465
63. Bero LA, Grilli R, Grimshaw JM, et al, on behalf of the Cochrane Effective Practice and Organisation of Care Review Group. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. BMJ 1998;317:465–468
64. Solberg LI. Guideline implementation: what the literature doesn't tell us. Jt Comm J Qual Improv 2000;26:525–537
65. Randall G, Taylor DW. Clinical practice guidelines: the need for improved implementation strategies. Healthc Manage Forum 2000; 13:36–42

