CME ACTIVITY

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CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Recognize partially-treated patients with bipolar disorder, e.g., residual symptoms of mood lability, irritability, or poor concentration.
- Demonstrate that using combination medication therapies (i.e., two mood stabilizers) may lead to clinical improvement without an increase in side effects.
- Realize that even in patients with more complex medication regimens it is feasible to follow a treatment algorithm.
- Predict that even in patients with long history of illness, continued empiric trials and particularly combination treatments are reasonable and may lead to substantial clinical improvement.
- Demonstrate both the importance of a clinical trial of a new medication for an adequate duration and dose/blood level and the importance of attending side effects in an effort to maximize compliance.

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Faculty Disclosure

In the spirit of full disclosure and in compliance with all Accreditation Council for Continuing Medical Education Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:

Dr. Suppes has received grant support from Abbott Laboratories, Parke-Davis, SmithKline Beecham Pharmaceuticals, Eli Lilly & Company, Glaxo Wellcome Inc., Novartis, Ortho-McNeil, and Organon Inc. and is a member of the speakers bureau for Abcomm.

Dr. Rush has received grant support from and is a consultant and member of the speakers bureau for Bristol-Myers Squibb Company, Eli Lilly & Company, Glaxo Wellcome Inc., Janssen Pharmaceutica, Novartis, Organon Inc., Pfizer Inc., Pharmacia & Upjohn, and Wyeth-Ayerst Laboratories.

Dr. Kraemer has no significant relationships with any entity that may have influenced her presentation in any way.

Mr. Webb has received funding support from the Stanley Foundation Bipolar Network.

Discussion of Investigational Information

During the course of their talks and discussions in this *Journal*, faculty may be presenting investigational information about pharmaceutical agents that is outside Food and Drug Administration–approved labeling. This information is intended solely as continuing medical education and is not intended to promote off-label use of any of these medications. Please refer to page 96 for a list of indications of off-label usage describing any medication discussed in this enduring material that, in the authors' clinical estimation, is outside the manufacturer's current recommendations for standard prescribing practices.

Treatment Algorithm Use to Optimize Management of Symptomatic Patients With a History of Mania

Trisha Suppes, M.D., Ph.D., A. John Rush, Jr., M.D., Helena C. Kraemer, Ph.D., and Andrew Webb

Background: While monotherapy has significant limitations in bipolar disorder, few published data addressing alternatives exist. Treatment algorithms have been proposed, but none have undergone empirical evaluation. This study provides a systematic prospective, open evaluation of the effectiveness and tolerability of a treatment algorithm for patients with histories of mania.

Method: Twenty-eight symptomatic outpatients from a public mental health facility who were diagnosed as having either bipolar I or schizoaffective illness, bipolar type, entered the study. Minimum blood levels of lithium and divalproex sodium were defined. Medications were pushed to predetermined levels (as tolerated) before proceeding to the next algorithm step. Clinical symptoms were assessed monthly using the Brief Psychiatric Rating Scale (BPRS, 27 item) and Clinical Global Impressions scale.

Results: Pretreatment and posttreatment clinical symptoms were compared. Over 50% of patients attained 30% improvement from baseline BPRS after 4 months. Thirty-six percent of patients (N = 10) became mood stable, 46% (N = 13) remained mood unstable, and 18% (N = 5) dropped out before completing the algorithm. Although patients who finished the algorithm were taking more medication, either dosage and/or drugs, somatic complaints did not increase.

Conclusion: The potential benefit of a defined treatment algorithm was demonstrated for these complex and persistently ill patients. Despite long treatment histories, patients improved with more frequent visits and addition of medication(s). A randomized controlled trial comparing a similar treatment algorithm with treatment-as-usual is warranted.

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Bipolar disorder was historically considered a remitting illness, believed to be responsive to lithium monotherapy. Recently, major revisions in diagnostic definition prompted the inclusion of patients previously diagnosed as schizophrenic.[1–3] This classification shift quite likely contributes to increasing disappointment with lithium treatment and other monotherapies. Prophylactic and maintenance trials are limited.[4,5] Naturalistic data examining outcomes of bipolar patients treated with lithium indicate that long-term prophylaxis is poor,[6–10] even when full remission follows initial treatment.[11] Recent reviewers suggest that noncompliance may be underestimated, while degree of prophylactic lithium efficacy may have been overestimated in earlier studies.[12] Unfortunately, although recognition of the limitations of long-term monotherapy is developing, few scientific data exist that suggest alternative therapies. It is unclear, for example, when to combine mood stabilizers, or even whether combination treatment is superior to monotherapy.[13–19]

One alternative to single-drug/restricted-dose treatments used in randomized controlled efficacy trials is to evaluate multiple treatments organized in a specified, sequenced fashion (a treatment algorithm). A treatment algorithm is a series of treatment steps defined by the patient's clinical response to the preceding step(s).[20] The major distinction between guidelines and algorithms is the level of specificity involved in each. Guidelines, when relying largely on scientific data, list treatment options accompanied by the level of supporting evidence to suggest the efficacy, safety, or tolerability, for example, the APA Guidelines on Bipolar Disorder.[21] As noted by Rush and Prien,[22] exclusive reliance on science leaves large gaps in our knowledge that preclude further specificity without reliance on at least clinical experience or clinical guidance from basic pharmacology and pathophysiology. When this clinical information is used to fill in the gaps in knowledge, more specific, sequenced steps of recommended treatment, each being recommended conditionally on the results of the prior steps, form what we have called algorithms.

Advantages to utilizing an algorithm-based treatment approach include simulation of actual treatment decision trees and clinician and patient latitude in choice and combination of medications. Once an algorithm's effectiveness is demonstrated, implementing research findings in routine practice should require minimal translation. Furthermore, the algorithm-based approach may prove effective in heterogeneous populations, such as bipolar-related disorders, because it provides individualized treatment.[23]

While traditional randomized controlled trials remain the gold standard of efficacy evaluation, the double-blind efficacy trial rarely mimics real-world clinical habits.[24] Other discrepancies include minimization of sample heterogeneity, short-term follow-up, and treatment delivery that seldom correspond with outpatient practice. To more closely ally clinical practice with research design, the algorithm-based approach may provide an alternative source of clinically relevant information.

The number of available medications is rapidly expanding. However, the possibility of completing double-blind controlled trials to evaluate each potential medication combination is remote. Several algorithms have been proposed,[4,14,25–28] but none have undergone empirical examination.

Limited agreement exists over which sources of heterogeneity effect treatment responses. For example, it is unclear whether anticonvulsants will be as treatment nonspecific for mood instability as antipsychotics are for psychotic symptoms, or whether matching between a specific anticonvulsant and a specific symptom complex will develop. Multiple medications are often necessary; therefore, effective treatment is itself heterogeneous.

As a prelude to a randomized trial, to gauge the tolerability and clinical impact of a four-step medication treatment algorithm, we evaluated a treatment algorithm in an open prospective fashion under representative clinical conditions in 28 symptomatic patients with a history of mania who were diagnosed as having either bipolar I or schizoaffective disorder, bipolar type. Of particular focus was the generation of hypotheses allowing more treatment options and sample heterogeneity than traditional randomized controlled trials. For example, could a defined treatment algorithm be applied to persistently ill bipolar patients? Would multiple mood stabilizers be efficacious with this population? Would multiple medications improve psychiatric symptoms yet exacerbate side effects?

METHOD

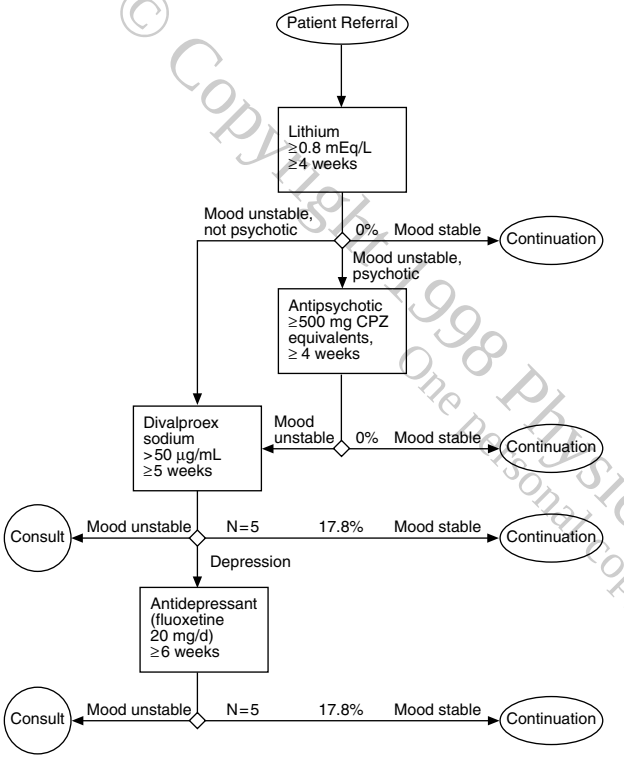
Sample

The primary referral source was the Dallas County Mental Health Mental Retardation outpatient clinics. Medical records and interviews with patients, past caregivers, and family members were obtained to confirm diagnosis and treatment history. Most patients (N = 27) received a structured clinical interview (SCID).[29,30] Entry criteria included history of mania, DSM-IV diagnosis of schizoaffective disorder, bipolar type, or bipolar I disorder,[21] and current, persistent symptoms including dysphoric hypomania, mood instability, irritability, and depression despite treatment. Entry decisions were based on clinical judgment of need to treat, not prespecified symptom rating scale minimums. Patients were excluded if they had a diagnosis of substance dependence or abuse in the 2 months prior to screening or a history of overt noncompliance defined by two or more missed clinic visits over the most recent 6 months. Study procedures and possible side effects were fully explained to patients, and written informed consent was obtained. Thirty-one patients were recruited. One patient signed consent, but did not return; two patients came to only one visit. The database consisted of 28 patients who made at least two visits.

Treatment Algorithm

The algorithm was designed a priori and intended to mimic best estimate clinical care for severely and persistently ill patients. All treatment decisions were clinically based and made by one of the three study psychiatrists in consultation with the principal investigator (T.S.). The al-

Figure 1. Treatment Algorithm: Minimum Time and Blood Levels Indicated and Patient Responses



gorithm (Figure 1) targeted mood stabilizers or antidepressants for specific symptoms of bipolar disorders: hypomania/mania and depressive symptoms (including sleep, energy, appetite), mood lability, poor concentration or distractibility, and psychotic symptoms. Symptoms of anxiety or panic, obsessive-compulsive symptoms, or personality disorders were not addressed with medication. Medication use outside the specified algorithm followed clinical discretion.

The algorithm rules follow: A patient entering on a medication regimen had that medication(s) optimized by the algorithm. For example, if a currently symptomatic bipolar I subject entered on lithium therapy (blood level < 0.6 mEq/L) and an antipsychotic (300 mg of chlorpromazine equivalents), lithium was increased until a blood level of ≥ 0.8 mEq/L was reached. If the patient was still psychotic, the antipsychotic was increased to ≥ 500 mg of chlorpromazine equivalents. If intolerable somatic complaints developed, the greatest tolerated dose of each medication was used, and medication(s) was added as specified if his or her mood remained unstable (see Figure 1). However, if a patient entered the study on well-documented minimum-accepted lithium levels (i.e., > 1 month of stability with levels available), the next algorithm step could be initiated immediately (e.g., start divalproex sodium).

Minimum time was required at each algorithm step once accepted blood levels of lithium or divalproex sodium were reached (Figure 1). Carbamazepine (blood level > 7.0 µg/mL) was considered a reasonable substitute for divalproex sodium if patients were taking that medication at study entry (N = 5). If a patient at entry was taking only an anticonvulsant, that monotherapy was optimized prior to adding lithium. Since this study was designed as a naturalistic trial, patients did not necessarily have to begin at the first line of the algorithm. For example, if a patient was already taking an anticonvulsant (either divalproex sodium or carbamazepine), then lithium was added. In such a case, the patient would begin the algorithm at the third stage, as displayed in Figure 1.

To establish if a given medication could be classified as clinically relevant (i.e., potentially affecting symptomatic outcome), minimum doses were set. Medication doses below the following were deemed unlikely to have mood changing or stabilizing value on the basis of literature review and consensus agreement (T.S., A.J.R). Minimum doses per day for antipsychotic medication were less than 50 mg of chlorpromazine equivalents; for lithium, less than 600 mg; for divalproex sodium, less than 500 mg; and for carbamazepine, less than 300 mg. For antidepressants, the following thresholds were set: desipramine less than 100 mg, trazodone less than 200 mg, bupropion less than 225 mg, and sertraline less than 50 mg. No minimums were set for fluoxetine (no patient received less than 20 mg/day) or paroxetine (no patient received less than 20 mg/day). Benzodiazepines, considered adjunctive, had no minimums.

Clinical Evaluation and Outcome Procedures

Patients were evaluated at entry and monthly using symptom rating scales. Nonrated clinic visits were allowed if needed. Symptom scale evaluators (two nurses) were not blind to patient treatment or study status. Symptom rating scales included the Brief Psychiatric Rating Scale (BPRS, 27-item),[31] Clinical Global Impressions scale (CGI),[32] and a self-report somatic complaints or side effects checklist. This 40-item checklist included a range of somatic complaints: nausea, headache, drowsiness, dizziness, tremor, change in weight, etc. The reliability correlation between nurses was > 0.8.

Decisions concerning study entry or discharge were based on team consensus and clinical assessment of

symptoms—independent of formal rating scales. Similarly, clinical decisions on moving to the next step in the algorithm were separate and independent from the outcome evaluations (e.g., BPRS).

The team carrying out this study met frequently to discuss all patients, and charts were reviewed three to four times a month throughout the study to track the evaluators' compliance. The principal investigator (T.S.) met with the physicians implementing the algorithm and provided monthly feedback on their adherence to the specifics.

To assess treatment success, patients were stratified by clinical outcome based on clinical judgment of the first author (T.S.), the treating psychiatrist, and the nursing staff: mood stable, mood unstable, or premature discontinuation. The clinical outcome stratifications were made independently from information provided by the BPRS or CGI. Patients were retained an additional month prior to discharge to confirm clinical status. Patients assessed as "mood stable" and transferred back to the clinic were considered unlikely to benefit from further mood-stabilizing medication changes. Clinical consensus was that patients defined as "mood unstable," with persistent symptoms of their affective illness, would benefit from further medication trials beyond the algorithm. *Premature discontinuation* refers to patients who discontinued without physician assent before receiving sufficient medication treatment for clinical evaluation.

Statistical Analysis

Changes between posttreatment and pretreatment BPRS and CGI scores were tested using matched-pairs t tests, and 95% confidence intervals for the change were computed. Significance values (p values) are provided only to estimate the magnitude of effect. Finally, utilizing clinical outcome definitions, survival distribution functions were analyzed using the Kaplan-Meier (product-limit) method.[33] All statistical computations were calculated using Statistical Analysis System software, release version 6.04.[34]

RESULTS

Study recruitment occurred over 18 months. The division of the sample by sex was almost even, and most patients were of Anglo-European descent (Table 1). All patients had clear histories of psychiatric illness, with a median time from first treatment of 15 years (Table 2). Most (N = 18) had been hospitalized within the last 2 years. Only a third (36%; N = 10) had recent employment, with fewer still working full-time (25%; N = 7). A portion received some disability (29%; N = 8), and few lived independently (25%; N = 7).

Table 1. Demographic Summary of 28 Symptomatic Bipolar I and Schizoaffective Patients

Characteristic	N	% of Total Population
Ethnic/gender groups		
White		
Women	15	54%
Men	10	36%
Total	25	90%
Black		
Women	1	4%
Men	2	7%
Total	3	11%
Psychosis		
Psychotic at entry	5	18%
Previously psychotic	20	71%
Never psychotic	3	11%
Total	28	100%
Diagnostic group		
Schizoaffective disorder	6	21%
Bipolar I disorder	22	79%
Manic (296.4)	3	11%
Mixed (296.6)	10	42%
Depressed (296.5)	9	46%
Total	28	100%

Table 2. Treatment History of Illness

Variable	Median	25%–75% Range	Range
Age, y	39	34–47	28–62
Age at first symptoms, y	17	13–20	6–35
Age at first treatment, y	24	19–33	7–58
Age at first hospitalization, y	26	21–35	7–50
Number of hospitalizations last 2 y	1	0–2	0–6
Lifetime hospitalizations	3	1–8	0–17

The majority of patients met criteria for bipolar I disorder (79%), and many patients were in the depressed or mixed phases at study entry (Table 1). Most had had psychotic episodes when acutely ill, and 5 were experiencing psychotic symptoms at study entry. Fifty-seven percent (N = 16) reported past substance abuse.

All patients were symptomatic at study entry and, except for 2, receiving ongoing medications. The BPRS total was greater than 45 at study entry for all patients except one (BPRS = 35). This patient (> 10 hospitalizations) entered during a relatively asymptomatic period while experiencing intolerable medication side effects.

Patients entering in a depressed state (DSM-IV, 296.5) did not, in general, do well. While meeting DSM-IV criteria for bipolar I, depressed phase (N = 9), all were experiencing mood lability, irritability, and hypomanic symptoms lasting less than 4 days, thus failing to meet

Table 3. Distribution of Psychiatric Symptoms From Baseline to End of Study*

	Baseline			Final			Change		
Patient Group	25%	50%	75%	25%	50%	75%	25%	50%	75%
All patients (N = 28)	51.5	61.5	75	44	49	53.5	–25	–14	–3
Mood stable (N = 10)	58	66	74	42	50	53	–11	–16	–27
Mood unstable (N = 13)	51	60	72	46	49	54	–19	–5	2
Premature discontinuation (N = 5)	51	60	84	44	45	46	–26	–16	–9

*Baseline and Final columns show distribution quartiles (25th percentile, median, 75th percentile) on the Brief Psychiatric Rating Scale (BPRS). The Change columns show distribution quartiles after subtracting each subject's baseline BPRS score from final BPRS score, i.e., within-subject score shown in quartiles.

mixed-phase criteria. These patients might not be considered typical bipolar I depressed-phase patients.[4] In total, 2 were discharged as mood stable. The remaining 7 were discharged as mood unstable (N = 6) or prematurely discontinued (N = 1). All other study patients (i.e., not entering in a depressed state) (N = 19) entered while experiencing hypomania with euphoria or in a mixed state, so overall results reflect these patients' response.

Clinical symptom assessment reflected overall improvement (Table 3). For all 28 patients, the BPRS change from study entry to discharge suggested a significant impact from study participation (p = .0001, CI = 8 .31 to 21.47), and for the CGI (p = .0003, CI = 0.25 to 0.75, data not shown).

Ten patients (36%) were discharged as mood stable, 13 (46%) continued as mood unstable, and 5 (18%) prematurely discontinued. No significant relationship was detected between age at onset, past history of hospitalization or other demographic factors, and likelihood of being discharged in a particular outcome category.

When patients were stratified by clinical outcome, there was marked improvement in the BPRS from study entry in the mood-stable group (BPRS: p = .001, CI = 9.02 to 25.38; and CGI: p = .02, CI = 0.10 to 1.10, data not shown). The premature discontinuation group showed a similar trend, but the number of subjects was too small and time in study too brief to evaluate relative impact of the algorithm.

Patients averaged 5.2 months in the study. Patients discharged to the mood-stable group generally spent longer in the algorithm (7 months), whereas the mood-unstable patients moved through more quickly (4 months). Patients discharged as premature discontinuation were not in the study long: 1 missed scheduled visits, 1 was medication noncompliant, 1 abused psychotropic substances, and 2 requested transfer prior to algorithm completion.

Survival analysis (Kaplan-Meier) was used to evaluate the impact of different definitions of treatment success. Over 50% of patients attained a greater than or equal to 30% reduction from baseline in BPRS total score by 4 months, while greater than 40% of patients evidenced a 40% reduction by 4 months.

A transition matrix of major medications illustrates the shift in medication use during the study (Figure 2). Forty-six percent of patients (N = 13) entered the study while taking two or more medications, but 79% (N = 22) completed the study as such. The primary new medication was an anticonvulsant (50%, N = 14). A large number of patients had lithium discontinued (25%, N = 7). All patients who entered the study on the triple combination of lithium, anticonvulsant, and antipsychotic therapy continued taking it. Patients overall took more drugs at study completion than at study entry.

Adjunctive antidepressant use was not extensive. Eleven patients, irrespective of entry diagnosis, entered on or received an antidepressant during the study. Five experienced remission in symptoms and were designated mood stable.

Patients adhered to the algorithm as shown by medication use self-report and blood levels. Blood levels targeting algorithm medications (lithium, carbamazepine, and divalproex sodium) were monitored, on average, once in every three visits, or 37% of the time.

Side effects did not appear related to patient dropout. Both absolute number (p = .36, CI = 1.36 to 3.57) and severity of reported side effects (p = .20, CI = 1.55 to 7.49) did not significantly change during the study for either the total group or any subset of the group (Table 4). For these persistently and severely ill patients, the addition of more medication, which often improved symptoms, did not increase incidence or severity of existing medication side effects.

DISCUSSION

Many questions posed at the study outset were answered. Patients with well-defined histories of mania and ongoing symptom complaints were relatively easy to locate in a public health setting. Particularly evident was the severe and persistent disability of the patients. Not only were patients experiencing symptoms of illness, including depression, mood lability, irritability, and poor concentra-

Figure 2. Medication Use From Study Entry to Discharge*†

Medication at Study Entry	Medication at Study Discharge									
Frequency	No Medication	Lithium	NL	AC	Lithium + NL	Lithium + AC	AC + NL	Lithium + NL + AC	Total N	%
No Medication	…	…	…	1	…	1	…	…	2	7%
Lithium	…	…	…	1	1	4	…	…	6	21%
NL	…	…	…	…	…	…	1	…	1	4%
AC	…	…	…	3	…	1	1	1	6	21%
Lithium + NL	…	…	…	…	…	…	4	1	5	18%
Lithium + AC	…	…	…	1	…	1	…	1	3	11%
AC + NL	…	…	…	…	…	…	2	…	2	7%
Lithium + AC + NL	…	…	…	…	…	…	…	3	3	11%
Total N	0	0	0	6	1	7	8	6	28	100%
%	0%	0%	0%	21%	4%	25%	29%	21%	100%	

*Abbreviations: AC = anticonvulsant, NL = neuroleptic, … = not applicable. Medications at study entry are read along a row and are summarized in the far right column; medications at study termination are read down columns and summarized along the bottom row. For example, while 6 patients entered on lithium monotherapy, no patient completed on lithium alone. To determine the changes in medications for these specific 6 patients, read across the row labeled lithium. Of these 6 patients, 1 changed to anticonvulsant monotherapy, 1 to lithium plus a neuroleptic, and 4 to lithium plus an anticonvulsant.
†Eleven patients entered on or received an antidepressant meeting threshold dose for clinical effectiveness during the study. Fifteen patients received some form of benzodiazepine during the study, with mean dose of 1.63 mg/day of clonazepam or 2.25 mg/day of lorazepam. Only 4 patients received benzodiazepines throughout their entire participation in the study (6 months on average).

Table 4. Distribution of Somatic Complaints From Baseline to End of Study*

	Baseline			Final			Change		
Patient Group	25%	50%	75%	25%	50%	75%	25%	50%	75%
All patients (N = 28)	6	11	15.5	6	10	14.5	–4	–1	–3.5
Mood stable (N = 10)	8	11	12	9	12	15	–6	–2.5	–3
Mood unstable (N = 13)	7	12	17	6	9	19	–4	–1	4
Premature discontinuation (N = 5)	5	6	14	6	8	12	–3	–1	0

*Baseline and Final columns show distribution quartiles (25th percentile, median, 75th percentile) of the number of somatic complaints endorsed on a 40-item, self-report somatic or side effect checklist. The Change columns show distribution quartiles after subtracting each subject's baseline BPRS score from final BPRS score, i.e., within-subject score shown in quartiles.

tion, but their lives lacked stability of housing, income, or relationships.[35]

Patient adherence to the treatment algorithm was determined by self-report and blood drug levels. Patient retention in the study (82%) was reasonable, given the severe and persistent nature of these patients' illness. The retention may have partially resulted from treatment flexibility inherent in the algorithm design. While compliance was not formally measured, increase of symptoms or lack of treatment response was investigated with blood levels and discussion with patients. The frequency of visits was substantially higher than in usual care, up to once a week versus once every 1 to 3 months, respectively. Another factor that may have enhanced adherence was that somatic complaints did not prompt study discontinuation; rather, the algorithm made alternative treatment choices available.

As a group, patients experienced decreased psychiatric symptoms when medications were added. Particularly striking was the rapid degree of improvement observed with the addition of an anticonvulsant, in most cases divalproex sodium. This finding supports the claim that even the more severely and persistently ill patient may benefit from additional medication changes. However, this open feasibility study precludes an evaluation of the relative contributions of changing medication and an increased frequency of visits.

The BPRS proved useful as an overall gauge of psychiatric wellness, although it was nonspecific for the target symptoms of the algorithm. Even though a patient could be termed mood stable for specific target symptoms, e.g., mood lability/irritability/etc., any elevation in BPRS symptom rating scores could have been due to persistent nontarget symptoms, e.g., somatic concerns, guilt not due to a mood disorder, anxiety, etc. Future studies will want to include specific mood symptom scales to evaluate the impact of an algorithm and to better inform the clinician when algorithm steps should or should not be taken.

While patients' overall symptoms improved with the initiation of more complex psychopharmacologic regimens, many patients did not enter full remission. Over 40% of patients were offered further medication changes,

i.e., those deemed mood unstable at algorithm completion. Another 4 were noncompliant, suggesting they received limited benefit from the algorithm. Thus, while both primary and subsyndromal symptoms were improved with additional medications, a more expanded treatment algorithm will be needed to provide improved treatment for many patients.

It may not be surprising that few patients responded to lithium alone or failed to improve at early points in treatment. The algorithm was not designed to address these issues, but to apply a broad treatment approach to a heterogeneous and severely ill population.

One unexpected finding was the lack of change in somatic complaints or side effects with use of more medication. Algorithm participation was not associated with an increase in somatic complaints. Thus, the judicious use of multiple medications appears well tolerated. Even in a more expanded algorithm, only limited guidelines may be needed to manage side effects.

The algorithm presented here was designed to mimic clinical practice. While the algorithm had face validity, a number of pragmatic issues emerged. Physicians adhered to the algorithm, but with some variability. For example, once minimum blood levels for lithium and/or divalproex sodium were met, partial response and symptom improvement were common. However, continued dose increases were completed over variable duration. While the treatment algorithm was anticipated to take 1 to 4 months, the addition of an antidepressant and/or partial response to medication at a low therapeutic level led to a mean study participation of 5.2 months. What precisely constituted drug intolerance was ill-defined. Finally, the issue of tapering primary medications (lithium, divalproex sodium, carbamazepine), especially in the absence of affective symptoms, was not systematized. These issues will need to be addressed in future studies.

This study will help develop treatment manuals for a randomized study. The construction of a manual should not simply increase the step specifics to be followed by clinicians, but provide recommendations with alternatives at each step.

A number of implications may be drawn regarding the use of multiple medications in this persistently ill patient group. Some patients may have clinically significant benefit from the addition of more medication. To date, little scientific literature has addressed the need for polypharmacy in bipolar patients, other than the rapid-cycling subtype.[36] In bipolar treatment in general, early preliminary and small case series have suggested that the use of multiple mood stabilizers may be efficacious for some treatment-resistant patients.[16,37–39] Recently, supportive data have indicated multiple medications are safe and well tolerated.[17] This is one of the first studies, to our knowledge, that provides a systematic prospective, although open, evaluation using multiple mood stabilizers in a persistently ill general population of bipolar patients.

There are constraints to the present study design, including its application to a heterogeneous patient population and the naturalistic, relatively uncontrolled use of medications. Some limitations include an open design, a lack of random selection, and treatment decisions based exclusively on clinical judgment rather than preset symptom scale values. As defined in the algorithm, the only regulated medications were primary mood stabilizers, antidepressants, or antipsychotics.

A strength of this study type is that findings should be more readily transferable to outpatient settings.[40] Usual clinical practice closely mimics study procedures, since study treatment decisions were based on symptoms and medication tolerability. The entry criteria allowed much greater heterogeneity within the sample than randomized controlled trial methodology, including history of significant comorbidity and complex symptom presentation.[22,24] Although this study was uncontrolled, useful clinical observations were made.

The potential to utilize a defined treatment algorithm was demonstrated for these persistently ill patients. This small, naturalistic study highlights that in a group of severely and persistently ill patients, a majority of patients experienced fewer psychiatric symptoms when medications were added to their treatment regimen. A randomized controlled trial comparing a treatment algorithm to treatment-as-usual is warranted to explore this design and develop treatment guidelines for multiple medication use with bipolar patients. We anticipate that such a study would include clinically based treatment decisions, with blinded outcome assessment of clinical symptoms, quality-of-life, and service use.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for treatment of bipolar disorder: typical antipsychotic agents for psychotic symptoms, and combination medication therapies (e.g., lithium and divalproex).

The following agent mentioned in this article is *not* indicated for treatment of conditions other than acute mania in psychiatric patients: divalproex.

Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 89 and correctly answering at least 70% of the questions in the quiz that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name, address, phone number, and fax number in the spaces provided.
3. Mail the Registration form along with a check, money order, or credit card payment in the amount of $10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
4. For credit to be received, answers must be postmarked by the deadline shown on the CME Registration form. After that date, correct answers to the quiz will be printed in the next issue of the *Journal*.

All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the quiz, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. It appears to be desirable to implement treatment algorithms for patients with a history of mania (e.g., DSM-IV bipolar I or schizoaffective illness, bipolar type). Some of the issues raised included the need for:
   a. An expanded algorithm to treat more severely ill patients
   b. Establishing guidelines for tapering medication once a patient stabilized
   c. Systematizing what constitutes an adequate clinical trial once a new medication is introduced
   d. Answers a and b only
   e. Answers a, b, and c only

2. In this group of patients with severe and persistent psychiatric illness:
   a. Patients generally did not improve clinically with the use of a second medication
   b. Patients developed more side effects when two or more medications were used
   c. Despite long-term illness, the majority of these patients were employed full-time and lived independently
   d. All of the above
   e. None of the above

3. Patients with a history of mania and currently experiencing symptoms of their illness:
   a. Showed rapid and significant clinical improvement with the addition of an anticonvulsant (usually divalproex sodium)
   b. Were proof that lithium alone was an adequate therapy for most bipolar patients
   c. Were proof that the use of combination medications was generally well-tolerated
   d. Answers a and c only
   e. Answers a, b, and c only

4. The use of two primary mood stabilizers with or without a typical antipsychotic:
   a. Led to study dropout
   b. Was well tolerated
   c. Led to nonadherence of prescribed medications
   d. Did not help
   e. Led to adverse medical events

5. The use of combination medication in bipolar patients:
   a. Is scientifically well established
   b. Is approved by the U.S. Food and Drug Administration
   c. Is a clinically dangerous practice
   d. May lead to substantial clinical improvement
   e. All of the above

6. Future trials of treatment algorithms for bipolar patients should include:
   a. More treatment options
   b. Less flexibility
   c. Individualized treatment
   d. Answers a and c only
   e. Answers a, b, and c only

7. Whether patients with improved clinical stability were able to make gains in other areas of their life (e.g., housing or employment):
   a. Is unknown
   b. Should be studied in an expanded trial
   c. Is unimportant
   d. All of the above
   e. Answers a and b only

Answers to the August 1997 CME quiz

1. e	3. b	5. c	7. e
2. d	4. c	6. d	

Circle the one correct answer for each question.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e
4.	a	b	c	d	e
5.	a	b	c	d	e
6.	a	b	c	d	e
7.	a	b	c	d	e

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Please evaluate the effectiveness of this CME activity on a scale of 1 to 5 (1 being poor, 5 being excellent).

1. Overall quality of this CME activity ____
2. Content ____
3. Format ____
4. Faculty ____
5. Achievement of educational objectives:
   - A. Enabled the reader to recognize partially-treated patients with bipolar disorder, e.g., residual symptoms of mood lability, irritability, or poor concentration. ____
   - B. Enabled the reader to demonstrate that using combination medication therapies (i.e., two mood stabilizers) may lead to clinical improvement without an increase in side effects. ____
   - C. Enabled the reader to realize that even in patients with more complex medication regimens it is feasible to follow a treatment algorithm. ____
   - D. Enabled the reader to predict that even in patients with long history of illness, continued empiric trials and particularly combination treatments are reasonable and may lead to substantial clinical improvement. ____
   - E. Enabled the reader to demonstrate both the importance of a clinical trial of a new medication for an adequate duration and dose/blood level and the importance of attending side effects in an effort to maximize compliance. ____
6. This CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias. ____
7. Please comment on the impact that this CME activity might have on your management of patients.

   _____

   _____

   _____

   _____
8. Please offer additional comments and/or suggested topics for future CME activities.

   _____

   _____

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