The Expert Consensus Guideline Series

Medication Treatment of Bipolar Disorder 2000

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The Expert Consensus Panel for Bipolar Disorder

The following participants in the Expert Consensus Survey were identified from several sources: recent research publications and funded grants, the DSM-IV advisers for mood disorders, the Task Force for the American Psychiatric Association's *Practice Guidelines for the Treatment of Patients with Bipolar Disorder*, and those who have worked on other mood disorder guidelines. Of the 65 experts to whom we sent the bipolar disorder survey, 58 (89%) replied. The recommendations in the guidelines reflect the aggregate opinions of the experts and do not necessarily reflect the opinion of each individual on each question.

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Contents

Preface

McGraw-Hill Healthcare Information Programs is pleased to publish the latest revision of The Expert Consensus Guideline Series: *Medication Treatment of Bipolar Disorder 2000*. The practice guidelines described in this publication have employed the latest survey techniques and reflect only the most current clinical standards. The result is a practical reference tool not only for clinicians but also for mental health educators and other healthcare professionals involved in the care of patients who have bipolar disorder. These guidelines, assembled under the expert direction of the editors (Gary Sachs, M.D., David J. Prinz, M.D., David A. Kahn, M.D., Daniel Carpenter, Ph.D., and John P. Docherty, M.D.), are designed to be easy to follow and use.

Treating patients with bipolar disorder is never easy, and the array of pharmacologic interventions can be difficult to understand and deploy. These guidelines offer a "one stop" reference. They deal with the initial and long-term management of common scenarios as well as complicated treatment issues. Interventions for the specific types of bipolar disorder—mania, bipolar depression, and rapid-cycling bipolar disorder—are outlined in detail. Initial and secondary options are presented for each type of disorder, along with advice regarding multiple- vs. single-drug therapy, side effects, and inadequate response to therapy. The section *A Guide for Patients and Families* (page 97), which includes information, resource groups, and a reference list, is exceptionally well done and will be practical for use by both groups. It will also serve as a helpful primer for primary care physicians.

The printed publication will now become a valuable addition to my reference library. I hope you find the guidelines to be beneficial in the care of your patients.

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Introduction: Methods, Summary, and Commentary

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ABSTRACT

Objectives. **New treatments for bipolar disorder have been reported since we first published survey-based expert consensus guidelines in 1996. The evidence for these treatments varies widely; data are especially limited regarding comparisons between treatments and how to sequence them. We therefore undertook a new survey of expert opinion in order to bridge gaps between the research evidence and key clinical decisions.**

Method. **Based on a literature review, a written survey was prepared which asked about 1,276 options for psychopharmacologic interventions in 48 specific clinical situations. Most options were scored using a modified version of the RAND Corporation 9-point scale for rating appropriateness of medical decisions. We contacted 65 national experts, 58 of whom (89%) completed the survey. Consensus on each option was defined as a non-random distribution of scores by chi-square test. We assigned a categorical rank (first-line/preferred choice, second-line/alternate choice, third-line/usually inappropriate) to each option based on the confidence interval of its mean rating. Guideline tables indicating preferred treatment strategies were then developed for key clinical situations.**

Results. **The expert panel reached consensus on many key strategies, including acute and preventive treatment for mania (euphoric, mixed, and dysphoric subtypes), depression, and rapid cycling, and approaches to managing the complications of treatment resistance and comorbidity.**

Use of a mood stabilizer is recommended in all phases of treatment. Divalproex (especially for mixed or dysphoric subtypes) and lithium are the cornerstone choices among this class for both acute and preventive treatment of mania. Regardless of which is selected first, if monotherapy fails, the next recommended intervention is to use these agents in combination. The combination can then serve as the foundation on which other medications are added, if needed. Carbamazepine is the leading alternative mood stabilizer for mania. Expert opinion regards other new anticonvulsants as second-line options (e.g., if the previously mentioned mood stabilizers fail or are contraindicated).

For milder depression, a mood stabilizer, especially lithium, may be used as monotherapy. Divalproex and lamotrigine are other first-line choices. For more severe depression, a standard antidepressant should be combined with lithium or divalproex. Bupropion, selective serotonin reuptake inhibitors (SSRIs), and venlafaxine are preferred antidepressants, and should be tapered 2 to 6 months after remission. Divalproex monotherapy is recommended for initial treatment of either depression or mania with rapid cycling.

Antipsychotics are recommended for use with the above regimens for mania or depression with psychosis, and as potential adjuncts in non-psychotic episodes. Atypical antipsychotics, especially olanzapine and risperidone, were generally preferred over conventional antipsychotics. Recommendations are also given concerning the use of electroconvulsive therapy (ECT), clozapine, thyroid hormone, stimulants, and various novel agents for patients with treatment-refractory illness.

Conclusions. **The experts reached high levels of consensus on key steps in treating bipolar disorder despite obvious gaps in high-quality data. To evaluate many of the treatment options in this survey, the experts had to extrapolate beyond controlled data; however, their recommendations are generally conservative. Experts reserve strongest support for initial strategies and individual medications for which there are high-quality research data, or for which there are longstanding patterns of clinical usage. Within the limits of expert opinion and with the understanding that new research data may take precedence, these guidelines provide clear pathways for addressing common clinical questions in a manner that can be used to inform clinicians and educate patients regarding the relative merits of a variety of interventions. (Postgrad Med Special Report. 2000(April):1–104)**

WHY A REVISION?

When we published the first *Expert Consensus Guidelines for the Treatment of Bipolar Disorder*[1] in 1996 (based on surveys completed in 1995), we were aware that new research and the introduction of new treatments might soon require us to revise them. The 2000 *Guidelines* are our first update. We based them on a survey of 58 leading experts on the medication treatment of bipolar disorder. Because the sheer number of potentially useful medications has made clinical decisions ever more complex, we elected to focus on medications and not to review options for psychosocial treatment. Readers may still refer to the earlier edition of the *Guidelines*[1] for information on psychosocial issues.

The contribution of expert consensus to practice guideline development continues to evolve throughout medicine, alongside the "gold standard" of meta-analysis of clinical trials and other experimental data. Developers of guidelines throughout medicine continue to struggle with the problem that the number of possible combinations and sequences of available treatments for many diseases makes

it difficult to establish practical guidelines based entirely on scientific data.[2, 3] Our group has developed a method for describing expert opinion in a quantitative, reliable manner to help fill some of the gaps in evidence-based guidelines. This method has been applied to a variety of psychiatric disorders.[1, 4–8]

METHOD OF DEVELOPING EXPERT CONSENSUS GUIDELINES

Creating the Surveys

We first created a skeleton algorithm based on a literature review. We sought to identify key decision points in the medication treatment of bipolar disorder as well as all the feasible treatment options. We highlighted important clinical questions that had not yet been adequately addressed or definitely answered.[9] A written questionnaire was then developed covering 48 specific clinical situations, divided into 166 subsections based on contingencies (e.g., subtypes, treatment history, comorbidity) with a total of 1,276 options for intervention. We began with questions concerning broad strategies, such as classes of medication, and then delved into tactics, such as specific medication selection and dosing. The survey took 2 or more hours to complete.

The Rating Scale

For 1,065 of the options in the survey, we asked raters to evaluate appropriateness by means of a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.[10] (The 211 other options asked raters to fill in a blank, such as dosage or duration of treatment.) We explicitly asked the raters to consider both personal experience and research evidence (we did not provide a literature review) in making their ratings, but not to consider financial cost. We presented the rating scale to the experts with the anchors shown in figure 1.

Figure 1. The Rating Scale

Extremely Inappropriate ← **1 2 3 4 5 6 7 8 9** → Extremely Appropriate

9 = Extremely appropriate: this is your treatment of choice

7–8 = Usually appropriate: a first-line treatment you would often use

4–6 = Equivocal: a second-line you would sometimes use (e.g., patient/family preference or if first-line treatment is ineffective, unavailable, or unsuitable)

2–3 = Usually inappropriate: a treatment you would rarely use

1 = Extremely inappropriate: a treatment you would never use

Figure 2 shows an excerpt from Survey Question 1 as an example of our question format.

Figure 2. Sample Survey Question

1. ***Treatment of mania: first episode, initial strategy.*** A physically healthy person in his or her 20s presents with a first manic episode severe enough to warrant hospital admission, or a first hypomanic episode severe enough to pose a likely eventual threat to functioning if unchecked. Based on the dominant symptom pictures shown below, please rate each of the following overall strategies as an initial intervention, assuming the patient is willing to take oral medication. (Subsequent questions will ask you about specific medications within the broad classes.)

Euphoric Mania

Mood stabilizer alone	1 2 3 4 5 6 7 8 9
Antipsychotic alone	1 2 3 4 5 6 7 8 9
Mood stabilizer + antipsychotic	1 2 3 4 5 6 7 8 9
Benzodiazepine alone	1 2 3 4 5 6 7 8 9
Benzodiazepine + mood stabilizer	1 2 3 4 5 6 7 8 9
Benzodiazepine + mood stabilizer + antipsychotic	1 2 3 4 5 6 7 8 9

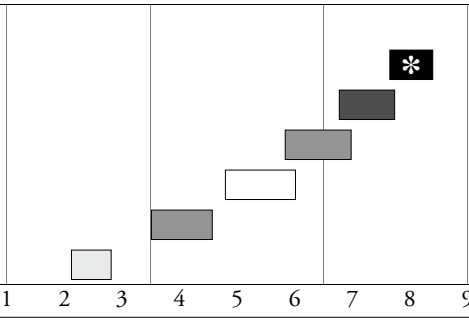
Selecting the Expert Panel

We identified 65 leading American experts in bipolar disorder through the following sources: authors of important publications in the past 5 years, recipients of research grants from government or industry, and members of American Psychiatric Association task forces for bipolar disorder practice guidelines and the affective disorders section of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). We excluded individuals who had previously declined to complete surveys for us. We sought to include both new and established clinical investigators.

Data Analysis for Options Scored on the Rating Scale

For each option, we first defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a chi-square test ($P<0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, 7–9). Next we calculated the mean and 95% confidence interval (CI). A categorical rating of first-, second-, or third-line was designated based on the lowest category in which the CI fell, with boundaries of 6.5 or greater for first-line, and 3.5 or greater for second-line. Within first-line, we designated an item as "treatment of choice" if at least 50% of the experts rated it as 9.

Figure 3. Results of the Euphoric Mania Section of Survey Question 1



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Euphoric Mania					
Mood stabilizer alone	8.0(1.4)	*57*	88	13	0
Mood stabilizer + benzodiazepine	7.3(1.8)	*36*	75	20	5
Mood stabilizer + antipsychotic	6.4(2.2)	*15*	58	26	16
Mood stabilizer + benzodiazepine + antipsychotic	5.4(2.3)	*6*	40	33	27
Antipsychotic alone	4.0(2.0)	*2*	13	38	49
Benzodiazepine alone	2.5(1.3)	*0*	0	13	88
		%	%	%	%

Displaying the Survey Results

The results of Question 1 (figure 2) are presented graphically in figure 3. The confidence intervals (CIs) for each treatment option are shown as horizontal bars and the numerical values are given in the table on the right. (The display of all of the results can be found in the survey results section, pages 50–96.)

The Ratings

First-line treatments are those strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatment for a given situation. ***Treatment of choice***, ✻ when it appears, is an especially strong first-line recommendation (having been rated as "9" by at least half the experts). In choosing between several first-line recommendations, or deciding whether to use a first-line treatment at all, clinicians should consider the overall clinical situation, including the patient's prior response to treatment, side effects, general medical problems, and patient preferences.

Second-line treatments are reasonable choices for patients who cannot tolerate or do not respond to the first-line choices. Alternatively, a second-line choice might be used for initial treatment if the first-line options are deemed unsuitable for a particular patient (e.g., because of poor previous response, inconvenient dosing regimen, particularly annoying side effects, general medical contraindication, potential drug-drug interaction, or if the experts don't agree on a first-line treatment).

For some questions, second-line ratings dominated, especially when the experts did not reach any consensus on first-line options. In such cases, to differentiate within the pack, we label those items whose CIs overlap with the first-line category as "high second-line."

Third-line treatments are usually inappropriate or used only when preferred alternatives have not been effective.

No consensus. For each item in the survey, we used a chi-square test to determine whether the experts' responses were randomly distributed across the 3 categories, which suggests a lack of consensus. These items are indicated by an unshaded bar in the survey results.

Statistical differences between treatments. While we did not perform tests of significances for most treatments, the reader can perform an "eyeball" test by looking to see whether the CIs overlap (indicating no significant difference between options by *t*-test). The wider the gap between the CIs, the smaller the *P* value would be (i.e., the more significant the difference). In some questions there are striking and important differences within levels, which we occasionally point out. Often, however, the differences within levels are not significant from a statistical perspective. Also, there are sometimes no statistical differences between choices rated at the bottom of first-line and those at the top of second-line.

From Survey Results to Guidelines

After the survey results were analyzed and ratings assigned, the next step was to turn these recommendations into user-friendly guidelines. We distinguish 2 levels, *preferred* options and *alternate* options, that generally correspond to first- and higher second-line ratings. Whenever the guideline gives more than 1 treatment in a rating level, we list them in the order of their mean scores. As an example, the full results of the question presented above are shown on page 50 and are used in *Guideline 1: Initial Strategy for a First Manic Episode* (page 16). A mood stabilizer as monotherapy is the preferred initial approach for most types of mania, while a mood stabilizer plus an antipsychotic was clearly preferred for mania with psychosis. As mentioned in

the legend, bold italics indicate treatment of choice rating, an especially strong opinion. The clinician might try these approaches, but move to the combinations with adjunctive medications if the patient could not be managed with monotherapy. Note that the choice of adjunct—benzodiazepine or antipsychotic—differs with the subtype of mania.

Summary of Results

The complete set of data from the survey is presented on pages 50–96. The guidelines derived by the editors from the data are presented on pages 16–46. Graphic treatment algorithms summarizing the expert recommendations are provided on pages 14–15. We summarize the highlights here.

Who were the panelists? Of the 65 national experts we contacted, 58 (89%) completed the survey. Of the 58 completers, 35 (60%) had also completed the 1996 survey. The average panelist was 49 years old (standard deviation, 9.3). Most of the panelists (80%) carry out their research and practice activities in non-Veterans Administration, non-governmental academic medical centers, typically spending about 25% of their time actually seeing patients; 94% of the panel participated in clinical research on bipolar disorder in the past 5 years. Most of the panelists had seen between 20 and 100 bipolar patients in clinical trials in the past year and had treated additional bipolar patients outside clinical trials.

What was the degree of consensus? Consensus was reached on 950 (89%) of the 1,065 options that used the rating scale. At least 1 first-line option was identified in 146 (88%) of the 166 subsections. Those areas in which no first-line options were identified all involved complex comorbidities or treatment-refractory illness.

What are the key recommendations? In terms of clinical practice, the single most important recommendation is to ***use a mood stabilizer in all phases of treatment***. Divalproex and lithium are the cornerstone choices among this class for both acute-phase and preventive treatment. They should be tried first when monotherapy is desired, in combination when either has failed, and as the bedrock upon which other medications may be layered. The leading alternative mood stabilizers are carbamazepine, especially for mania, and the newer agent lamotrigine, especially for depression. The next major finding is that ***when an antipsychotic is needed, atypicals are generally preferred over conventionals for initial treatment***. The only presentation where conventionals join atypicals as a first-line option is mania with psychosis. A third important finding is that ***mild depression should be treated with mood stabilizer monotherapy initially, while severe depression should be treated from the start with an antidepressant plus a mood stabilizer***. However, after resolution of a first episode of bipolar depression, antidepressants should be tapered in 2 to 6 months, a much shorter continuation period than is generally advised for non-bipolar depression. A fourth finding is that ***either mania or depression with rapid cycling should be treated initially with a mood stabilizer alone***, preferably divalproex for either phase. The top-rated choices for initial medication treatment are shown in table 1.

Table 1. Top-Rated Choices for Initial Medication
(Assumes no contraindications; adjunctive medications added subsequently if indicated)

Euphoric mania or hypomania	Lithium or divalproex
Mixed or dysphoric mania	Divalproex
Mania with psychosis	Divalproex or lithium with antipsychotic (atypical or conventional)
Milder depression	Lithium
More severe depression	Lithium or divalproex with antidepressant (plus atypical antipsychotic if delusional)
Mania or depression with recent rapid cycling	Divalproex

Key comparisons with the last survey. Support for the use of divalproex has increased. Ratings for lithium and carbamazepine remain stable. Lamotrigine, which was included in this survey for the first time, received positive ratings for the treatment of bipolar depression. In an important switch, atypical antipsychotics are now generally rated ahead of conventionals. Finally, venlafaxine received significantly stronger ratings in this survey and joined bupropion and SSRIs in the group of first-line antidepressants.

Key comparisons with recent literature. While panelists were not asked to review the literature in order to answer the survey, we have informally evaluated the degree to which their recommendations are supported by evidence. (It is interesting to note that a comparison of the 1996 *Guidelines* with evidence-based guidelines from the American Psychiatric Association and other sources revealed no contradictions, but differences in emphasis and in degree of specificity.[11]) The experts mostly favored treatments for which high-quality data, such as methodologically sound, placebo-controlled trials, are available. They showed intermediate or less support for treatments for which only less rigorous studies and case reports are available. Even so, there are many situations for which there are no well-controlled data, such as key drug-drug comparisons or the management of illness that is refractory to first-line treatments. In these situations, the panel did not display strong

preferences—rather they supported the reasonableness of trying those options for which there was some evidence. For the treatment of refractory illness, they prefer combining or switching to established treatments (including ECT and clozapine) before experimenting with less established medications.

COMMENTARY

What do the new survey results tell us about the state of optimum practice in treating bipolar disorder? In this section, we discuss similarities and changes since our last survey in 1995 and consider the relationship between opinion and evidence in the experts' key decisions.

Mood Stabilizers for Mania

Just as in 1995, divalproex and lithium are still the highest rated first-line treatments for all subtypes of mania. Lithium's numerical scores were unchanged, while scores for divalproex increased: scores for divalproex are now nearly indistinguishable from those for lithium in mania with euphoric mood, and divalproex is preferred as the treatment of choice for both mixed and dysphoric mania. These findings are consistent with the results of a large-scale prospective clinical trial comparing divalproex, lithium, and placebo in acute mania[12] and *post hoc* analyses of response by subtype.[13] Carbamazepine, as in the last survey, remains the most favored alternative mood stabilizer, a result that is consistent with it being the only other non-antipsychotic medication that has been shown to be effective for mania in well-designed studies.[14] Lamotrigine received, at best, low second-line ratings as an initial treatment, reflecting the preliminary nature of the evidence for its efficacy[15] and perhaps concern about the need for slow titration of dosage to minimize the risk of rashes. Gabapentin was rated mostly a third-line choice, which is consistent with the lack of high-quality research.[16] Its strongest ratings are for comorbid panic disorder, and as an add-on therapy to other mood stabilizers. Controlled data for gabapentin are unlikely to be published, given the absence of positive findings. Further studies are unlikely, perhaps owing to the imminent expiration of its patent and consequent lack of commercial potential. Its apparent popularity among clinicians may be more for bipolar II disorder (the survey focused more on bipolar I disorder). A related anticonvulsant, pregabalin, which is not yet available, may receive more rigorous research. Among treatments that have been anecdotally reported to be helpful, topiramate and calcium channel blockers were rated as appropriate for patients who are resistant to other treatments, although not for initial therapy. There was some support for the omega-3 fatty acids but no overall consensus on their usefulness, while tiagabine was viewed as generally not helpful. Antipsychotic monotherapy was not highly recommended except for possible use in psychotic mania; we will discuss the use of antipsychotics in more detail in a later section of this introduction.

Bipolar Depression

The lack of data on major depression in bipolar disorder makes it a difficult topic to address in evidence-based guidelines, but an interesting one on which to examine the consensus of opinion. The experts' recommendations concerning the treatment of depression without rapid cycling have shifted somewhat since 1995. The experts now lean more toward the use of a mood stabilizer alone for milder initial episodes. Just as in 1995, however, they recommend adding an antidepressant from the start for severe depression and would also add an antipsychotic or give ECT for psychotic depression.

The first choice of mood stabilizer for monotherapy for depression is lithium. However, in contrast with the 1995 survey results, divalproex (not well studied for this use) and lamotrigine were both also rated first-line, although below lithium. It should be noted that lamotrigine is the only medication that has been shown to be effective for bipolar depression in a large, randomized, controlled clinical trial,[17] except for studies from decades earlier that showed benefit from lithium.

It is interesting that the choice of mood stabilizer changes when it is to be combined with an antidepressant: lamotrigine drops from the first-line group, and divalproex rises nearly to the level of lithium. This suggests an emphasis on using tried-and-true mood stabilizers to guard against antidepressant-induced switches to mania. Only the top choice, lithium, has been well tested in this situation, and was found to protect against mania when combined with imipramine in a long-term maintenance study.[18]

A new topic we asked about in the current survey was breakthrough depression (i.e., an episode of depression that occurs while a patient is on maintenance treatment with lithium or divalproex). In this situation, the experts favor first maximizing doses of lithium or divalproex. Divalproex, lamotrigine, or antidepressants are equally ranked as add-ons if lithium monotherapy fails, another clear indication of the growing role for lamotrigine.

Concerning the choice of specific antidepressants, there are few data on which the panel could base their opinions. As in the last survey, bupropion and SSRIs are among the first-line choices for initial therapy, and bupropion is especially favored for more moderate depression. (The available SSRIs all received roughly comparable ratings.) It should be noted that venlafaxine is now rated as a first-line option, especially for more severe depression; its rating has moved up considerably since 1995 when it had just been introduced. Monoamine oxidase inhibitors are still a favored backup and received equal ratings with nefazodone and mirtazapine. As before, tricyclics are the least favored antidepressants but received a few strong votes for more severe depression.

In a new question, we asked about strategies for patients who had not responded to an SSRI. There was strong consensus to switch to bupropion (treatment of choice) or alternatively to venlafaxine (first-line), rather than to try another SSRI. Bupropion was voted the least likely to cause a switch to mania both in first episode patients and in those with a history of switching to mania while taking other antidepressants. This result is consistent both with the last survey and with its being the only antidepressant that has been studied prospectively with this question in mind.[19]

For depression that does not respond to an initial treatment regimen of a mood stabilizer plus an antidepressant, the panel's confidence in lithium is underscored by the recommendation that it be added to any regimen that does not include it—especially to augment a partial response. As in 1995, the panelists did not have any clear-cut recommendations concerning other augmentation strategies, although they appear to suggest this sequence:

- try an anticonvulsant if the patient is not taking one (divalproex tied with lamotrigine, carbamazepine next, then gabapentin)

  or
- try another antidepressant
- add thyroid hormone (T3 preferred over T4)
- add a stimulant
- add an atypical antipsychotic, possibly clozapine

  or

  for seasonal depression, use phototherapy.

As in mania, a host of unproved treatments (dopamine agonists, omega-3 fatty acids, sleep deprivation, topiramate, nimodipine, inositol, buspirone), for which there are only anecdotal reports, received equivocal ratings, with the least support for phenytoin and St. John's wort.

Rapid Cycling

For the manic phase of rapid cycling, divalproex, which was rated treatment of choice in 1995, received still higher ratings in the current survey. Lithium moved up to a first-line alternative for non-dysphoric cases, while carbamazepine remained the other major first-line choice. In the depressed phase of rapid cycling, which we did not explicitly ask about in 1995, divalproex monotherapy was rated treatment of choice, and lamotrigine and lithium were tied as lower first-line choices. Antidepressants should be added only if mood stabilizers fail. The strong consensus concerning treatments for rapid cycling is generally consistent with the results of open studies and retrospective analyses. These show that divalproex and carbamazepine are superior to lithium,[20, 21] especially in mania, and that lamotrigine is more beneficial in depression than in severe mania.[22] Gabapentin received modest support for rapid cycling. Atypical antipsychotics were a favored add-on for treatment-refractory mania or depression with rapid cycling, an approach that is supported only by case reports.

Long-Term Preventive Treatment

The panel supported using either lithium or divalproex or a combination of both, whatever worked during the acute phase of treatment, for long-term prevention after a manic episode. Lithium's efficacy for prevention is well established based on data from the 1970s (although more recent data also indicate substantial failure rates). The confidence in divalproex reflects clinical experience; it has been harder to obtain controlled evidence for divalproex in maintenance treatment due to the difficulty of enrolling suitable patients in randomized, placebo-controlled studies.[23] Nonetheless, clinical reports and open, prospective studies show that divalproex, in some cases added to lithium or even used in triple therapy in combination with lithium and carbamazepine, may succeed in patients with treatment-refractory illness, including rapid cyclers.[24, 25] Although we did not ask about the use of carbamazepine as preventive treatment, small-scale studies have shown benefits for its use alone[26] and in combination with lithium.[27]

Atypical Antipsychotics

This discussion would not be complete without mentioning the growing role of atypical antipsychotics in the treatment of bipolar disorder, especially in light of the expected Food and Drug Administration approval of olanzapine for mania and earlier approvals of conventional antipsychotics for manic psychosis. In the current survey, atypical antipsychotics other than clozapine are now rated as first-line agents for adjunctive treatment of mania (as are benzodiazepines in non-psychotic cases). Atypical antipsychotics are also rated as first-line agents for combined treatment of psychotic depression, in contrast to the panel's preference for conventional antipsychotics in 1995. The current panel also strongly preferred atypicals when an antipsychotic is needed for long-term maintenance. Atypicals were also highly rated backups in any phase of rapid cycling. Conventional antipsychotics received first-line ratings only for psychotic mania or for patients with mania who have failed to respond to 1 or 2 atypical antipsychotics. Depot conventional antipsychotics received strong second-line support for the treatment of nonadherent patients. The results of the current survey are compatible with available data, including a pivotal study showing that olanzapine is more effective than placebo as monotherapy for mania,[28] growing evidence in support of risperidone,[29, 30] and preliminary experience with quetiapine.[31] The recent evidence also allays earlier fears of frequent "activation" by atypicals (although isolated instances may occur). These data, taken together with the lower risk of extrapyramidal side effects, support the panel's conclusions.

How should atypicals be sequenced in treatment? First, although the experts strongly support the adjunctive use of atypical antipsychotics, they still hesitate to recommend them over traditional mood stabilizers for monotherapy in mania. Second, for an adjunct to add to a mood stabilizer in hypomania, the panel prefers a benzodiazepine over an antipsychotic. The panel gives equal ratings to adjunctive benzodiazepines or antipsychotics in more severe mania without psychosis, and endorses antipsychotics as essential in psychotic mania. This recommendation—to reserve antipsychotics for more severe cases—is the same as in the last survey and is consistent with clinical tradition rather than clear-cut data.

As in the last survey, clozapine is well rated for any phase of treatment-resistant illness or for rapid cycling. These uses are supported by well-designed research.[32] Ziprasidone, although unapproved for use at the time of this survey, was favorably viewed by experts who had used it in clinical trials for various disorders. It was also mentioned as a good alternative for patients who have gained weight on other medications.

The role of atypical antipsychotics as add-on treatments and as primary mood stabilizers in different phases of bipolar disorder is an important current research area.

Dosing and Duration of Treatment

We did not ask about dosing in our previous survey. In the current survey, we found standard deviations of about 30% to 40% in recommendations for acute doses of carbamazepine, divalproex, and lithium and about 50% for long-term maintenance. The variances were even wider for lamotrigine, gabapentin, topiramate, and tiagabine. We were not surprised by the wide variances given the tremendous variability between individuals in metabolism, dose-response requirements, and tolerance for side effects. It is worth noting that there was greater agreement on doses of the more established agents, which is consistent with the availability of far more experimental data. As in the last survey, experts look for a quick response to a mood stabilizer in mania: if there is no response within a week, they would consider using another medication; if a partial response has reached a plateau after 2 weeks, the experts would begin to use another medication.

When initiating treatment of mania with divalproex, most experts suggest starting with a full therapeutic dose (e.g., 20 mg/kg/day), often referred to as a "loading dose." Consistent with this approach, the panel also believed that one might see results about a day or 2 earlier with divalproex than with other mood stabilizers (generally advising a wait of at least 1 to 2 weeks before adding another mood stabilizer). Adjunctive antipsychotics in mania were given less time to prove their mettle—a week or less before the experts recommend trying a second antipsychotic. The experts also were willing to combine atypical and conventional antipsychotics in treatment-resistant illness, consistent with a common, though experimentally untested, clinical practice.

We did not repeat a 1995 question on acute-phase doses of antidepressants. The recommendation in the earlier survey was to start low and go slow, but to aim eventually for the same maximum doses as in non-bipolar depression. For continuation antidepressant treatment, the experts reiterated their earlier advice to taper after 2 to 6 months of remission, compared with the 6 to 12 months commonly recommended for non-bipolar depression. There are few research data on dosing and duration of antidepressant treatment in bipolar disorder.

Electroconvulsive Therapy

The experts' enthusiasm for ECT has not diminished since 1995, despite the plethora of new medications. The panelists favor the use of ECT early in psychotic depression, preferring it to lithium augmentation. They would press for the use of ECT in nonpsychotic depression if the patient has had an inadequate response to treatment with 2 mood stabilizers, including a trial of lithium, plus 2 antidepressants. For a patient having a manic episode who has failed to respond to lithium and divalproex plus antipsychotics, the experts gave equal ratings to ECT or adding a third mood stabilizer. In several questions about treatment resistance or rapid cycling, many experts actually wrote in ECT as a preference for acute-phase or maintenance treatment even when we did not offer it as an option. ECT is well supported by research studies in mania[33] and depression.

CONCLUSIONS

Limitations and Advantages of Expert Consensus Guidelines

These guidelines can be viewed as an expert consultation, to be weighed in conjunction with other information and in the context of each individual patient-physician relationship. The recommendations do not replace clinical judgment, which must be tailored to the particular needs of each clinical situation. We describe groups of patients and make suggestions intended to apply to the average patient in each group. ***However, individual patients will differ greatly in their treatment preferences and capacities, history of response to previous treatments, family history of treatment response, and tolerance for different side effects. Therefore, the experts' first-line recommendations certainly will not be appropriate in all circumstances.***

We remind readers of several other limitations of these guidelines:

1. The guidelines are based on a synthesis of the opinions of a large group of experts. From question to question, some of the individual experts would differ with the consensus view.

2. We have relied on expert opinion precisely because we are asking crucial questions that are not yet well answered by the literature. One thing that the history of medicine teaches us is that expert opinion at any given time can be very wrong. Accumulating research will ultimately reveal better and clearer answers. Clinicians should therefore stay abreast of the literature for developments that would make at least some of our recommendations obsolete. We hope to revise the guidelines periodically based on new research information and on reassessment of expert opinion to keep them up-to-date.
3. The guidelines are financially sponsored by the pharmaceutical industry, which could possibly introduce biases. Because of this, we have made every step in guideline development transparent, reported all results, and taken little or no editorial liberty.
4. These guidelines are comprehensive but not exhaustive; because of the nature of our method, we omit some interesting topics on which we did not query the expert panel.

Despite the limitations, these guidelines represent a significant advance because of their specificity, ease of use, and the credibility that comes from achieving a very high response rate from a large sample of the leading experts in the field.

Guidelines Research

It is easy to get experts to agree on key steps, but how do we know they are right? Two major research projects illustrate the power of consensus guidelines and test their ability to improve care.

The first is the Texas Medication Algorithm Project (TMAP), a controlled, 2-year study of whether patients treated according to guidelines have better outcomes than patients receiving "treatment as usual" care.[34] The previous edition of *The Guidelines*[1] was the starting point for the bipolar disorder module.[35]

The second major project is the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sponsored by the National Institute of Mental Health. This project is based on the recognition that, at most of the decision points in this survey, more than 1 option is rated first-line, and that together these options represent a menu of reasonable options for clinical care. It is likely that this multiplicity of first-line options indicates a state of clinical uncertainty, which can be resolved only by high-quality empirical data. Over the next 5 years, STEP-BD will report outcomes for 5,000 bipolar patients in treatment centers around the United States which have agreed to implement a common intervention model based on various first-line expert recommendations.

Advances in public health do not always require technological breakthroughs or long periods of waiting for new data. Immediate gains can be made by increasing the frequency at which the best available known treatments are implemented. Guidelines offer a rapid means for communicating a distillate of expert opinion. When reaching a clinical decision point, practitioners and patients can use guidelines to generate a menu of reasonable choices and then select the option that is judged best for each individual. This process drives the next round of expert opinion and the next round of empirical studies.

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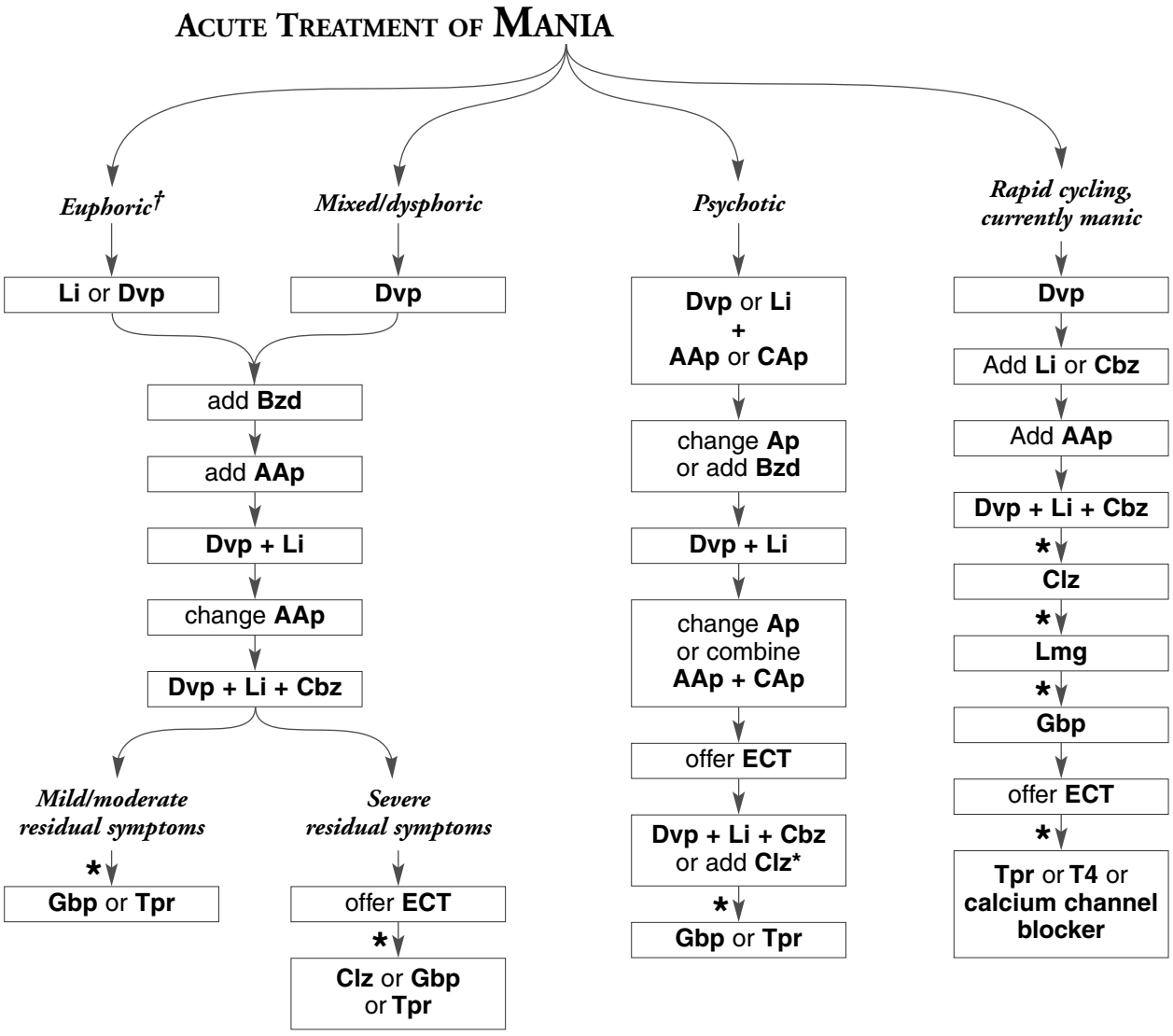


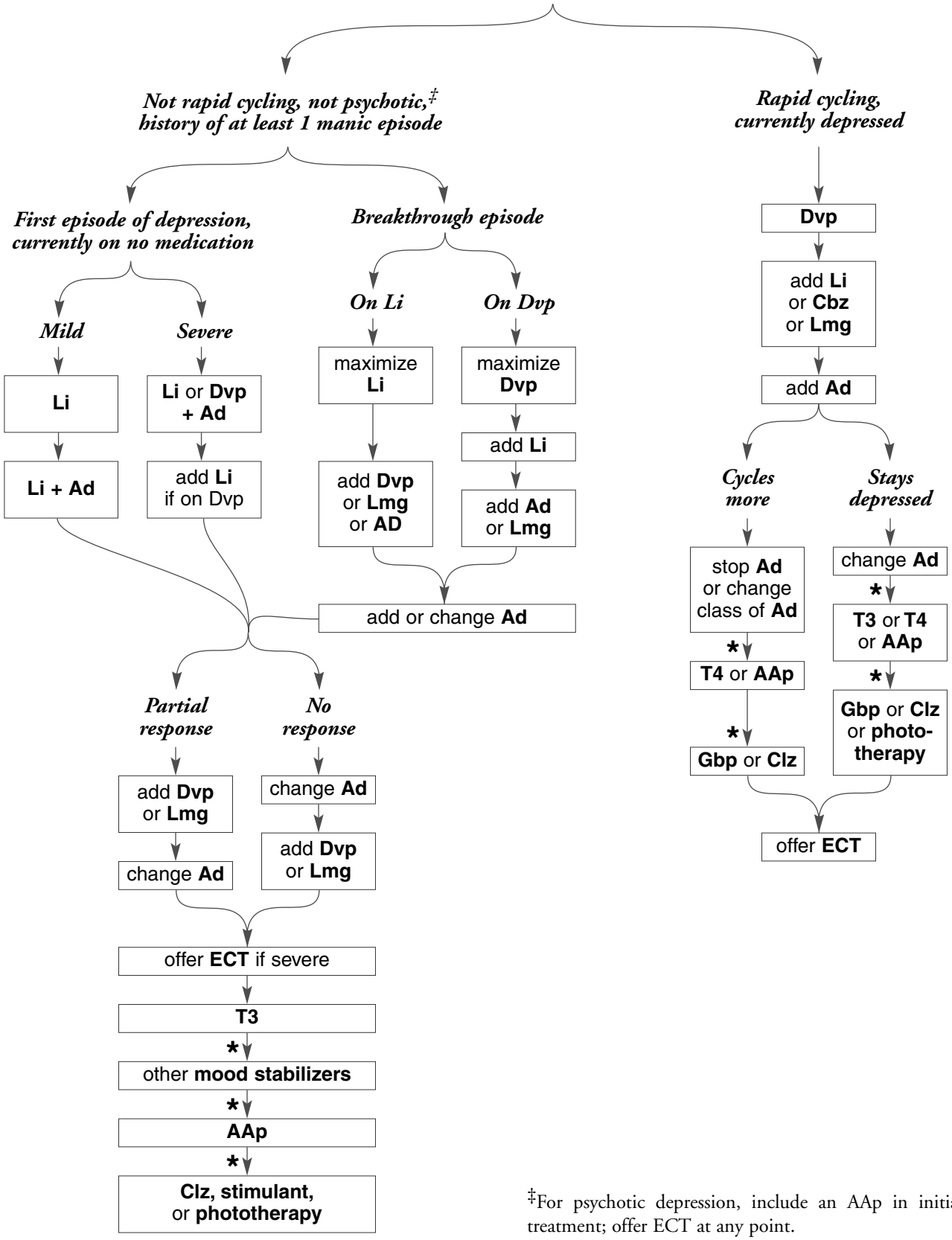
Legend

AAp	atypical antipsychotic
Ad	antidepressant
Ap	antipsychotic
Bzd	benzodiazepine
CAp	conventional antipsychotic
Cbz	carbamazepine
Clz	clozapine
Dvp	divalproex
ECT	electroconvulsive therapy
Gbp	gabapentin
Lmg	lamotrigine
Li	lithium
T3	triiodothyronine
T4	L-thyroxine
Tpr	topiramate

* When adding second-line medications, the clinician may wish to discontinue 1 or more of the previous medications. Clinicians should avoid combining carbamazepine and clozapine.

†Recommendations for hypomania are essentially the same as for euphoric mania, but with less support for the use of antipsychotics.

ACUTE TREATMENT OF BIPOLAR DEPRESSION



‡For psychotic depression, include an AAp in initial treatment; offer ECT at any point.

I. TREATMENT OF MANIA

Guideline 1: Initial Strategy for First Manic Episode

1A. Choice of Treatment Regimen[1]

The experts consider a mood stabilizer alone as the treatment of choice for mania or hypomania, except in mania with psychosis where combining the mood stabilizer with an antipsychotic is preferred. If an adjunct is needed in other types of mania, the experts prefer to use a benzodiazepine unless the severity of the symptoms requires an antipsychotic. Except in psychosis, there was no clear consensus on when to combine both an antipsychotic and a benzodiazepine with a mood stabilizer, although many experts believe it is sometimes appropriate. Note: In the survey, the term "mood stabilizer" was used to refer to lithium and anticonvulsants, but did not include atypical or conventional antipsychotics.

Bold italics = treatment of choice

Clinical presentation	**Preferred initial strategies**	**Alternate strategies**
Mania with psychosis	***Mood stabilizer + antipsychotic***	Mood stabilizer + antipsychotic + benzodiazepine
Dysphoric mania or true mixed mania*	***Mood stabilizer alone***	Mood stabilizer + benzodiazepine *or* Mood stabilizer + antipsychotic
Euphoric mania†	***Mood stabilizer alone*** *or* Mood stabilizer + benzodiazepine	Mood stabilizer + antipsychotic
Hypomania	***Mood stabilizer alone***	Mood stabilizer + benzodiazepine

Dysphoric mania*: patient has a manic episode and also meets 2 to 4 diagnostic criteria for depression, but is below threshold for a current diagnosis of a major depressive episode. ***True mixed mania*: patient meets full criteria for both a manic episode and a major depressive episode.

†***Euphoric mania***: patient has a manic episode without features of depression.

[1]Question 1

1B. Choice of Mood Stabilizer[2]

Divalproex and lithium were chosen from a large list of potential mood stabilizers as the clear standards of care. Divalproex is the treatment of choice for mania that is mixed, dysphoric, or includes psychosis. In these 3 conditions, lithium is the first-line alternative but with significantly lower mean scores than divalproex. Lithium is the treatment of choice for euphoric mania, although its mean rating did not differ significantly from that of divalproex, which is also a first-line option. Carbamazepine is a very highly ranked second-line alternative for all subtypes of mania. Only when these agents fail or cannot be used do the experts recommend treatment with lamotrigine or gabapentin. There was less support for topiramate, tiagabine, and calcium channel blockers.

Bold italics = treatment of choice

Clinical presentation	Preferred mood stabilizers*	Alternate mood stabilizer
Mania with psychosis	***Divalproex***	Carbamazepine
	Lithium	
Dysphoric mania or true mixed mania	***Divalproex***	
	Lithium	
Euphoric mania	***Lithium***	
	Divalproex	
Hypomania	Lithium	
	Divalproex	

*Note: The experts did not make a distinction between the immediate release and modified release formulations of lithium. Generic valproate received high second-line ratings.

[2]Question 2

1C. Choice of Antipsychotic[3]

Adding an antipsychotic to the mood stabilizer is the treatment of choice for mania with psychosis and may also be helpful in other types of mania. In all situations, olanzapine and risperidone were regarded as first-line choices by a majority of the experts, with the strongest support for olanzapine. In psychotic mania, high-potency conventional antipsychotics were also rated first-line by a majority of experts. However, overall, the atypical antipsychotics as a class were significantly preferred over the conventional antipsychotics. The practice of combining conventional and atypical antipsychotics as initial treatment received the lowest ratings.

Clinical presentation	Preferred antipsychotics	Alternate antipsychotics*
Mania with psychosis	Olanzapine	Mid-potency conventional antipsychotic
	High-potency conventional antipsychotic	Quetiapine
	Risperidone	
Euphoric mania, dysphoric mania, or true mixed mania	Olanzapine	A high- or mid-potency conventional antipsychotic
	Risperidone[†]	Quetiapine
Hypomania	*No first-line choice*	Olanzapine or risperidone if an antipsychotic is needed

*Ziprasidone was not available at the time of the survey, but experts who had used the drug in clinical trials felt that it might have value, particularly in mania with psychosis (see page 96).

[†]Rated very high second-line

[3]Question 3

Guideline 2: Next Step After Inadequate Response to Initial Strategy for First Manic Episode

2A: General Strategy for Next Step[4]

If the patient has had no response to the first mood stabilizer within 1 to 2 weeks, the experts recommend adding or switching to another top-rated mood stabilizer (see Guideline 1B). In contrast, if the patient is showing a partial response, the experts would simply add a second mood stabilizer after 2 to 3 weeks. The only exception to these time frames is when the initial treatment was lamotrigine, in which case the experts recommend extending the initial trial about a week longer. This may reflect the need for slower titration of lamotrigine doses.

Response	**Preferred strategy**	**How long to wait before making a change**
No response	Add or switch to another mood stabilizer	1–2 weeks
Partial response	Add another mood stabilizer	2–3 weeks

[4]Question 11 and Kahn D, Carpenter D, Docherty JP, et al. The expert consensus guideline series: treatment of bipolar disorder. J Clin Psychiatry 1996;57(Suppl 12A):17.

2B: Adding a Second Mood Stabilizer for a Partial Response[5]

When it is appropriate to combine mood stabilizers, the experts overwhelmingly recommend lithium as the next choice to add to any of the anticonvulsants. Divalproex is a first-line choice to add to lithium, gabapentin, or carbamazepine. After these, carbamazepine is preferred before turning to adjunctive gabapentin or lamotrigine. ***Note:*** See Guideline 4 for special instructions on combining divalproex with carbamazepine or lamotrigine.

Bold italics = treatment of choice

If initial treatment was	**Preferred mood stabilizers to add**	**Alternate mood stabilizers to add**
Divalproex	***Lithium***	Carbamazepine
Lithium	***Divalproex*** Carbamazepine	
Carbamazepine	***Lithium*** Divalproex	
Lamotrigine	***Lithium***	Divalproex
Gabapentin	***Lithium*** ***Divalproex***	Carbamazepine

[5]Question 4

2C: Strategies for Choosing Another Antipsychotic After a Failed Initial Trial[6]

If a patient is not responding to the combination of a mood stabilizer and an antipsychotic, it may be appropriate to change the antipsychotic earlier than the mood stabilizer. If the patient is having no response to an initial antipsychotic trial, the experts recommend waiting only 5 to 10 days before making a change. For a patient who is having a partial response, the experts recommend continuing the antipsychotic for 1 to 2.5 weeks before changing to another antipsychotic.

If initial class was	Preferred strategy*	Alternate strategy
Conventional antipsychotic	Switch to an atypical antipsychotic	Combine an atypical and a conventional antipsychotic
Atypical antipsychotic	Switch to a conventional antipsychotic *or* Switch to another atypical antipsychotic	

*Many experts commented that it is desirable to overlap (cross-titrate) the medications when switching from one antipsychotic to another.

[6]Questions 5 and 6

2D: Continued Treatment Resistance[7]

A combination of lithium and divalproex is an appropriate strategy for patients with mania who have not responded to monotherapy plus adjunctive antipsychotic and/or benzodiazepine. Should this combination strategy fail, the experts recommend continuing the current treatment and adding carbamazepine. In more severe cases of mania, other first-line options are to change the antipsychotic to clozapine or administer electroconvulsive therapy (ECT). In less severe mania, gabapentin is a second-line choice; there was no consensus on lamotrigine in refractory mania. In milder cases, it may be possible to simplify the treatment regimen by tapering 1 or more of the initial mood stabilizers while adding the new medication.

Present status	Preferred strategy	Alternate strategy
Mania with psychosis	Switch to ECT* *or* Continue present medication and add carbamazepine or clozapine	
Severe mania, not psychotic	Continue present medication and add carbamazepine *or* Switch to ECT*	Continue present medication and add clozapine *or* Taper and stop lithium and/or divalproex and add carbamazepine or clozapine
Moderate or mild residual symptoms	Continue present medication and add carbamazepine	Taper and stop antipsychotic and/or benzodiazepine and add carbamazepine or gabapentin *or* Taper and stop lithium and/or divalproex and add carbamazepine or gabapentin

*Many experts commented on the importance of maintenance ECT for patients whose mania has been difficult to control with medication.

[7]Question 7

2E: Other Approaches to Treatment-Resistant Mania[8]

When standard mood stabilizers and antipsychotics have to failed to produce an adequate response, and if ECT or clozapine is not suitable for a specific patient, clinicians may need to consider other approaches that have been reported as potentially helpful for treatment-resistant mania. None of the options we asked about achieved a first-line consensus. However, there was modest enthusiasm for topiramate, especially when used to augment another mood stabilizer. There was also some support for the use of nimodipine and other calcium channel blockers.

Consider in place of other mood stabilizers	**Consider as add-on to other mood stabilizers**
Topiramate	Topiramate
Nimodipine	Nimodipine
	Omega-3 fatty acids
	Calcium channel blocker other than nimodipine
	Tiagabine
	Adrenergic antagonist

[8]Question 8

Guideline 3: Maintenance Treatment After a Manic Episode

3A: Long-term Maintenance After a Manic Episode[9]

On the assumption that most patients will have received lithium, divalproex, or a combination of the 2 for an acute manic episode, we asked the panel whether this regimen should be continued or changed during long-term maintenance. In all cases, the treatment of choice was to continue the same regimen that had been effective during the acute phase. However, for patients who had had a significant history of depression prior to their first manic episode and had received divalproex alone for the manic episode, some experts would consider adding lithium to the maintenance regimen. Including an antidepressant in the maintenance regimen was a lower second-line option for patients with a history of depression.

Bold italics = treatment of choice

If acute phase treatment was	Preferred continuation treatment	Alternate strategy*
Lithium alone	***Lithium alone***	
Divalproex alone	***Divalproex alone***	Combine lithium and divalproex or use lithium alone for a patient with a history of severe depressions
Lithium + divalproex	***Lithium + divalproex***	

*Consider including an antidepressant for patients with a significant history of depression (rated lower second-line).

[9]Question 9

3B: Preferred Antipsychotics for Long-Term Maintenance in Combination With Mood Stabilizers[10]

It is common practice to taper antipsychotic medications following the resolution of acute manic symptoms. However, some patients may benefit from long-term treatment with antipsychotics. In this situation, the experts clearly prefer atypical antispychotics. Conventional antipsychotics received much lower ratings for long-term maintenance than they did for acute-phase treatment (see Guideline 1C). They may be needed, however, for patients who require a depot formulation because of adherence problems (see Guideline 10B). Although the experts would consider combining an atypical and a conventional antipsychotic during the acute phase for a patient having an inadequate response (see Guideline 2C), they do not recommend this combination strategy for long-term maintenance treatment.

Preferred antipsychotics	Alternate antipsychotic*
Olanzapine Risperidone	Quetiapine

*Ziprasidone was not available at the time of the survey, but most experts who had used the drug in clinical trials rated it more highly than conventional antipsychotics (see page 96).

[10]Question 10

3C: Strategies for Breakthrough Mania During Maintenance Treatment[11]

Patients maintained on 1 or more mood stabilizers may experience breakthrough episodes of mania.

If patients have been maintained on lithium or divalproex monotherapy, the first step is to increase the dose if possible. If the patient is already receiving lithium or divalproex alone at a maximum tolerable dose, the first choice would be to add another mood stabilizer. An alternative first-line strategy would be to add an adjunctive benzodiazepine or antipsychotic.

If a patient is already taking a combination of lithium and divalproex, the experts recommend either adding an adjunctive agent or a third mood stabilizer. For a patient who has breakthrough episodes on carbamazepine, the experts recommend increasing the dose. In contrast, for breakthrough episodes that happen with gabapentin or lamotrigine, the experts prefer adding another mood stabilizer that has better established efficacy.

Bold italics = treatment of choice

If current treatment is	**Preferred strategies**	**Alternate strategies**
Lithium alone—low dose	***Increase lithium***	Increase lithium and/or add another mood stabilizer
Lithium alone—high dose	Add another mood stabilizer *or* Add adjunctive treatment	
Divalproex alone—low dose	***Increase divalproex***	Increase divalproex and/or add another mood stabilizer
Divalproex alone—high dose	***Add another mood stabilizer*** *or* Add adjunctive treatment	
Lithium + divalproex at maximum tolerable doses	***Add adjunctive treatment*** *or* Add another mood stabilizer	
Carbamazepine	Increase carbamazepine	Increase the dose and/or add another mood stabilizer *or* Continue carbamazepine at the same dose and add adjunctive treatments
Gabapentin or lamotrigine	Add another mood stabilizer	Increase the dose and/or add another mood stabilizer or adjunctive agent *or* Switch to another mood stabilizer

[11]Questions 12 and 13

3D: Choice of Mood Stabilizers to Add for Breakthrough Mania[12]

When adding an additional mood stabilizer for breakthrough mania, the experts give essentially the same recommendations as for a patient who is having a partial response and focus on lithium or divalproex. For patients already receiving a combination of lithium and divalproex, carbamazepine is the preferred option to add on, followed by gabapentin. Otherwise, gabapentin and lamotrigine are lower rated options. ***Note:*** See Guideline 4 for special instructions on combining divalproex with carbamazepine or lamotrigine.

Bold italics = treatment of choice

If current treatment is	**Preferred mood stabilizers to add***	**Alternate mood stabilizers to add***
Lithium	***Divalproex*** Carbamazepine	
Divalproex	***Lithium***	Carbamazepine
Lithium + divalproex	Carbamazepine	Gabapentin
Carbamazepine	***Lithium*** Divalproex	
Gabapentin	***Lithium*** ***Divalproex***	Carbamazepine
Lamotrigine	***Lithium*** Divalproex	Carbamazepine

*See Guideline 4 for a discussion of potential drug interactions.

[12]Question 14

Guideline 4: Adequate Dose and Duration of Mood Stabilizers[13]

The table below presents the experts' recommendations for acute and maintenance doses of the various mood stabilizers and acute blood levels of lithium, divalproex, and carbamazepine.

For established agents (lithium, divalproex, and carbamazepine), the wide range of doses reflects the fact that there is great individual variation in the doses required to achieve recommended serum levels of these agents. Approximately two-thirds of the experts favor beginning with an initial dose of divalproex that targets the middle of the therapeutic range (often referred to as a "loading dose") in appropriate treatment settings. In contrast, the experts commented that the even wider dose ranges for the newer agents reflect current uncertainty about adequate dosing. In general, the experts prefer to use slightly lower doses during the maintenance phase of treatment.

Medication*	**Treatment of acute mania**			**Long-term maintenance**	
(Doses in mg/day unless otherwise noted)	**Average starting dose**	**LOW end of average target dose/level**	**HIGH end of average target dose/level**	**LOW end of average dose/level**	**HIGH end of average dose/level**
Carbamazepine dose	400 ± 100	600 ± 200	1400 ± 400		
Carbamazepine level, μg/mL		6.1 ± 2.6	12.6 ± 4.2	5.7 ± 1.5	10.8 ± 2.2
Divalproex or valproate dose	750 ± 375	750 ± 375	2750 ± 1000		
Divalproex therapeutic target dose	20 ± 3 mg/kg/day				
Valproic acid level, μg/mL		58.9 ± 14.9	120 ± 16.6	56.6 ± 12	109 ± 17
Gabapentin dose	700 ± 300	1200 ± 400	3200 ± 900	900 ± 400	2700 ± 900
Lamotrigine dose	25 ± 12.5	100 ± 50	300 ± 125	100 ± 50	250 ± 125
Lithium dose	900 ± 300	900 ± 300	2100 ± 600		
Lithium level, mEq/L		0.7 ± 0.1	1.2 ± 0.1	0.6 ± 0.1	1.1 ± 0.1
Tiagabine dose	4.0 ± 2.0	12 ± 8	32 ± 16	12 ± 8	24 ± 12
Topiramate dose	50 ± 25	125 ± 50	400 ± 250	125 ± 75	350 ± 175

*For convenience, we have adapted the raw data from the survey in the following manner: Mean doses and standard deviations have been rounded to available pill strengths. For blood levels, we have rounded values to be consistent with standard laboratory reporting practices.

Note on drug combinations:

When adding lamotrigine to divalproex, lamotrigine should be started at 50% of the usual starting dose and increased more slowly. Adding divalproex to full therapeutic doses of lamotrigine is more problematic because enzyme inhibition caused by divalproex is reported to cause a 2- to 3-fold increase in the half-life of lamotrigine. Clinicians are advised to consult the manufacturer's recommendations for the titration of lamotrigine (see *Physicians' Desk Reference*) to minimize the risk of inducing rash.

Adding divalproex to full therapeutic doses of carbamazepine is often problematic because free carbamazepine levels are reported to increase by 100% to 300% in the presence of divalproex. Adding carbamazepine to full therapeutic doses of divalproex is often better tolerated as long as the carbamazepine is titrated slowly.

[13]Question 11

II. TREATMENT OF BIPOLAR DEPRESSION

Guideline 5: Treatment of First Episode of Bipolar Major Depression

5A. Initial Strategy for First Episode of Bipolar Major Depression[14]

We asked the experts about a patient with a history of mania who has been stable for several years and is currently receiving no medication, but is experiencing a first episode of depression.

For mild to moderate depression or for a patient whose initial manic episode was precipitated by an antidepressant, the experts show a slight preference for treatment with a mood stabilizer alone, although combining a mood stabilizer and an antidepressant is a closely ranked alternative option.

For more severe depression, the experts clearly support combining an antidepressant with the mood stabilizer from the start (along with an antipsychotic for psychotic depression). ECT is another first-line option for severe depression with psychosis. A highly rated second-line option for severe psychotic depression is to combine a mood stabilizer and an antipsychotic. In all cases, the use of an antidepressant alone was rated as generally undesirable.

Clinical presentation	**Preferred initial strategies**	**Alternate strategies**
Severe depression with psychosis	Mood stabilizer + antidepressant + antipsychotic *or* ECT	Mood stabilizer + antipsychotic *or* Mood stabilizer + antidepressant
Severe depression without psychosis	Mood stabilizer + antidepressant	Mood stabilizer alone *or* ECT
Mild to moderate depression	Mood stabilizer	Mood stabilizer + antidepressant
Initial mania was precipitated by antidepressant treatment for supposed unipolar depression	Mood stabilizer	Mood stabilizer + antidepressant

[14]Question 15

5B. Choice of Antidepressant for First Episode of Bipolar Major Depression[15]

The ratings for the first-line and high second-line options were very close. For the most part, bupropion, venlafaxine, and the selective serotonin reuptake inhibitors (SSRIs) all received comparably high ratings for use in a first episode of major depression in combination with a mood stabilizer. Bupropion stood out as the treatment of choice in moderate depression. For severe atypical depression, monoamine oxidase inhibitors (MAOIs) were a highly rated second-line choice. In all situations except severe melancholic depression, tricyclic antidepressants (TCAs) were rated significantly lower than all the other antidepressants, including MAOIs.

Bupropion was clearly rated as the antidepressant least likely to precipitate an episode of mania in a patient who has never previously received an antidepressant. With the exception of the TCAs, all the other antidepressants, led by paroxetine, were felt to be relatively safe when used in combination with a mood stabilizer.

Bold italics = treatment of choice

Clinical presentation	**Preferred antidepressants**	**High second-line alternatives**	**Other second-line alternatives**
Severe melancholic depression with or without psychosis	Venlafaxine Bupropion Paroxetine	Sertraline Citalopram Fluoxetine	Fluvoxamine Mirtazapine MAOI TCA Nefazodone
Severe atypical depression without psychosis	Bupropion Paroxetine Sertraline Venlafaxine Citalopram	Fluoxetine MAOI Fluvoxamine	Nefazodone Mirtazapine
Mild to moderate depression	***Bupropion*** Paroxetine Sertraline Citalopram Fluoxetine Venlafaxine	Fluvoxamine	Mirtazapine Nefazodone MAOI
To avoid precipitating mania in a patient who has never previously received antidepressants	Bupropion Paroxetine	Nefazodone The other SSRIs Mirtazapine MAOI Venlafaxine	

Further Recommendation: Dosing of antidepressants: Antidepressants are to be used at the same target therapeutic doses and titrated upward at the same rate as in non-bipolar major depression ("unipolar depression").[16] However, for patients who have a history of being easily switched into mania or hypomania on antidepressants, clinicians may want to use more cautious dosing strategies.

[15]Questions 16 and 28

[16]Kahn D, Carpenter D, Docherty JP, et al. The expert consensus guideline series: treatment of bipolar disorder. J Clin Psychiatry 1996;57(Suppl 12A):53.

5C. Choice of Mood Stabilizer for First Episode Bipolar Major Depression[17]

For a first episode of depression in an unmedicated bipolar patient, lithium is the mood stabilizer of choice to use either alone or in combination with an antidepressant. Divalproex is a first-line alternative. Lamotrigine is also a first-line choice for use alone, but drops to high second-line for use in combination with an antidepressant. Carbamazepine is a highly rated second-line option for use either alone or in combination with an antidepressant. Gabapentin is a lower second-line option in both situations.

Bold italics = treatment of choice

For use	Preferred mood stabilizers	Alternate mood stabilizers
Without an antidepressant	***Lithium***	Carbamazepine
	Divalproex	
	Lamotrigine	
In combination with an antidepressant	***Lithium***	Lamotrigine
	Divalproex	Carbamazepine

[17]Question 17

5D: Choice of Antipsychotics for Bipolar Depression With Psychosis[18]

The 3 available atypical antipsychotics are preferred over the conventional agents, with olanzapine and risperidone being the first-line choices.

Preferred antipsychotics	Alternate antipsychotics*
Olanzapine	Quetiapine
Risperidone	High- or mid-potency conventional antipsychotic

*Ziprasidone was not available at the time of the survey, but most experts who had used the drug in clinical trials for other disorders rated it more highly than conventional antipsychotics (see page 96).

[18]Question 18

5E: Duration of Antidepressant and Antipsychotic Treatment[19]

Most experts recommend tapering antidepressants at some point after remission from a first episode of bipolar depression. For more severe depressions, they recommend continuing antidepressant treatment for 2 to 6 months beyond the point of remission before tapering, although about 25% of the experts would continue the antidepressant indefinitely. A slightly shorter period is recommended for patients with a less severe episode. If patients are also receiving an antipsychotic, the experts recommend continuing it for almost as long as the antidepressant; however, very few experts would continue it indefinitely.

How long to continue:	Weeks
An antidepressant for severe depression with or without psychosis	9–23
An antidepressant for moderate depression	8–20
An antipsychotic for severe psychotic depression	7–22

[19]Question 19

5F: Strategies for a First Episode of Depression as a Switch Immediately After a Manic Episode[20]

Patients sometimes switch into depression immediately following the resolution of a manic episode. In a newly diagnosed bipolar patient, it may not be possible to foresee and prevent such a switch. In this difficult situation, there was no consensus on first-line strategy. However, a number of strategies received higher second-line ratings. One option is simply watchful waiting for a few more weeks to see if the episode will resolve spontaneously. Other options depend on the patient's current regimen. For patients taking lithium, adding lamotrigine, divalproex, or an antidepressant is acceptable. For a patient taking divalproex alone, adding lithium is somewhat preferred, but adding an antidepressant or lamotrigine is also acceptable. For patients already taking a combination of divalproex and lithium, adding an antidepressant is somewhat preferred while adding lamotrigine is also acceptable. Adding thyroid and adding carbamazepine are lower rated alternatives.

The following clinical situation was presented to the experts:

- first episode of depression that occurred immediately following a first or second manic episode
- patient taking maximum tolerable doses of lithium and/or divalproex
- episode has progressed over 2 weeks to moderate severity
- patient is not suicidal or psychotic
- patient is euthyroid, has never taken antidepressants, and is receiving appropriate psychotherapy

If current treatment is	**Preferred strategies (none were first-line, no significant differences between options shown)**
Lithium alone	Add lamotrigine Add an antidepressant Watchful waiting Add divalproex
Divalproex alone	Add lithium Add an antidepressant Watchful waiting Add lamotrigine
Lithium + divalproex	Add an antidepressant Watchful waiting Add lamotrigine

[20]Question 20

5G: Strategies for a First Episode of Breakthrough Depression Delayed Some Time After a Manic Episode[21]

Management of the patient whose first episode of depression occurs after a prolonged remission poses somewhat different problems than the previous situation of an episode of depression that occurs immediately following a manic episode. Generally the experts prefer to intervene, although a significant minority still felt that watchful waiting for at least a few weeks was a preferred strategy. Since maintenance doses of mood stabilizers may be lower than acute-phase doses, the first recommendation is to ensure that the patient is receiving a maximal dose of either lithium or divalproex in monotherapy. If a combination of low-dose lithium and divalproex is already being used, either of the medications can be increased, although the preference is to maximize the lithium dose first. For a patient who has a breakthrough depression on a high dose of divalproex, the first-line choice is to add lithium, with the addition of lamotrigine or an antidepressant as high second-line options. For breakthrough on high-dose lithium, it is a toss-up whether to add an antidepressant, lamotrigine, or divalproex. For patients already receiving a combination of maximal doses of lithium and divalproex, the first-line strategy is to add an antidepressant, with the addition of lamotrigine a high second-line choice.

The following clinical situation was presented to the experts:

- first episode of depression that occurred after a significant period of stability (e.g., 3 to 6 months) following a first or second manic episode
- episode has progressed over 2 weeks to moderate severity
- patient is not suicidal or psychotic
- patient is euthyroid, has never taken antidepressants, and is receiving appropriate psychotherapy

Bold italics = treatment of choice

If current treatment is	Preferred strategies	Alternate strategy: Add one of the following
Lithium alone—low dose	***Increase lithium***	Divalproex Lamotrigine An antidepressant
Lithium alone—high dose	Add an antidepressant (high second-line) *or* Add lamotrigine or divalproex (high second-line)	
Divalproex alone—low dose	Increase divalproex	Lithium An antidepressant
Divalproex alone—high dose	Add lithium	An antidepressant Lamotrigine
Lithium + divalproex—both low dose	***Increase lithium*** *or* Increase divalproex	An antidepressant
Lithium + divalproex—both high dose	Add an antidepressant	Lamotrigine

[21]Question 21

Guideline 6: Inadequate Response to Initial Strategy for Bipolar Depression

6A: Bipolar Depression Without Psychosis: Strategies After an Inadequate Initial Response[22]

Adding an antidepressant is the treatment of choice for patients who have not responded to a mood stabilizer alone. Changing to another antidepressant is the treatment of choice for patients who have not responded to a combination of a mood stabilizer and an antidepressant. There is also strong support for lithium augmentation. Other important second-line alternatives are to add an anticonvulsant if the patient is taking lithium or to add thyroid hormone (T3 preferred over T4; see Guideline 9C). There was mixed opinion regarding augmentation with stimulants or atypical antipsychotics. Conventional antipsychotics are not recommended.

Bold italics = treatment of choice

Level of response	Preferred strategies	High second-line alternatives	Other second-line alternatives
If little or no response to:			
Mood stabilizer alone	***Add an antidepressant***	Add lithium if patient is taking an anticonvulsant *or* Add an anticonvulsant if patient is taking lithium	
Mood stabilizer + antidepressant	***Switch to a different antidepressant*** *or* Add lithium if patient is taking an anticonvulsant	Add an anticonvulsant if patient is taking lithium	Add thyroid *or* Change to another mood stabilizer while tapering the first
If partial response to:			
Mood stabilizer alone	***Add an antidepressant*** *or* Add lithium if patient is taking an anticonvulsant	Add an anticonvulsant if patient is taking lithium	
Mood stabilizer + antidepressant	Add lithium if patient is taking an anticonvulsant	Switch to a different antidepressant *or* Add an anticonvulsant if patient is taking lithium *or* Add thyroid	Change to another mood stabilizer while tapering the first

[22]Question 22

6B: Bipolar Depression With Psychosis: Strategies After an Inadequate Initial Response[23]

For those patients who are not considered candidates for ECT, the recommendations for psychotic bipolar depression that is showing little or no response are similar to those shown previously for nonpsychotic depression: adding or changing the antidepressant and augmenting with lithium. Adding an anticonvulsant if the patient is taking lithium or switching to a different antipsychotic are highly rated second-line options. Thyroid augmentation is a lower second-line option. Stimulants are not recommended for use in patients with psychotic depression.

Bold italics = treatment of choice

Level of response *If little or no response to:*	**Preferred strategies**	**Alternate strategies**
Mood stabilizer + antipsychotic	***Add an antidepressant*** *or* Add lithium if patient is taking an anticonvulsant	Add an anticonvulsant if patient is taking lithium *or* Switch to a different antipsychotic
Antidepressant + mood stabilizer + antipsychotic	Switch to a different antidepressant *or* Add lithium if patient is taking an anticonvulsant	Add an anticonvulsant if patient is taking lithium *or* Switch to a different antipsychotic Also consider adding thyroid hormone

[23]Question 23

6C: Bipolar Depression: Choice of Next Antidepressant[24]

Consistent with their recommendations for the initial treatment of an episode of bipolar depression, the experts also recommend adding or switching to bupropion, an SSRI, or venlafaxine if a patient is having an inadequate response. Note that if the initial medication was an SSRI, the experts are not enthusiastic about switching to another SSRI. If the initial treatment was venlafaxine, then bupropion is significantly preferred over an SSRI among the first-line options. The overall message is to add or switch to a second medication that is significantly *different* from the first medication. MAOIs, mirtazapine, and nefazodone generally received comparable ratings as second-line alternatives. There was no consensus regarding the use of TCAs.

Bold italics = treatment of choice

If little or no response to	Preferred medications to add or switch to	Alternate medications to add or switch to
Bupropion	***SSRI*** Venlafaxine	MAOI (after washout)* Mirtazapine Nefazodone
SSRI	***Bupropion*** Venlafaxine	Mirtazapine MAOI (after washout)* Nefazodone
Venlafaxine	Bupropion SSRI	Mirtazapine MAOI (after washout)* Nefazodone
Mirtazapine	Bupropion SSRI Venlafaxine	MAOI (after washout)* Nefazodone
MAOI *Note: Do NOT add other antidepressants to an MAOI. Stop MAOI for 2-week washout before starting another antidepressant.*	Bupropion	Venlafaxine SSRI Mirtazapine Nefazodone
Nefazodone	Bupropion SSRI Venlafaxine	Mirtazapine MAOI (after washout)*
TCA	Bupropion SSRI Venlafaxine	MAOI (after washout)* Mirtazapine Nefazodone

Further Recommendation: To avoid precipitating a manic episode in a patient who has had a prior episode of mania induced by an antidepressant of a particular class, the experts recommend bupropion as the first-line choice if not already tried, with the SSRIs and nefazodone rated high second-line (assuming that the prior episode of mania was not induced by an antidepressant of the same class). With the exception of the TCAs, the other antidepressants are all acceptable alternatives.[25]

*All antidepressant manufacturers recommend washout before beginning an MAOI. Some clinicians report that MAOIs may be cautiously added to mirtazapine, nefazodone, or a TCA provided there is close monitoring. In no case should an MAOI be combined with an SSRI or venlafaxine.

[24]Question 24 [25]Question 28

6D: Bipolar Depression: Choice of Next Mood Stabilizer[26]

This table shows the recommendations for a patient with moderate to severe depression who has had little or no response to treatment with an antidepressant plus a mood stabilizer (as well as an antipsychotic if psychosis is present). If the clinician has decided to add or switch to another mood stabilizer, lithium is the treatment of choice when the initial treatment was an anticonvulsant. Lamotrigine and divalproex are other first-line choices, while carbamazepine is a highly rated second-line option. Gabapentin is an acceptable second-line alternative. There is less support for adding another anticonvulsant when lamotrigine was the initial treatment, presumably because of concern about drug interactions.

Bold italics = treatment of choice

If little or no response to	Preferred medications to add or switch to	Alternate medications to add or switch to
Divalproex	***Lithium*** Lamotrigine	Carbamazepine Gabapentin
Lithium	Divalproex Lamotrigine Carbamazepine	Gabapentin
Carbamazepine	***Lithium*** Lamotrigine Divalproex	Gabapentin
Lamotrigine	***Lithium***	Divalproex Carbamazepine Gabapentin
Gabapentin	***Lithium*** Divalproex Lamotrigine	Carbamazepine

[26]Question 25

6E: Bipolar Depression With Psychotic Features: Choice of Next Antipsychotic[27]

The experts recommend switching to an atypical antipsychotic if the patient is having an inadequate response to a conventional antipsychotic or switching to a different atypical if the first atypical does not produce an adequate response. There was no consensus on combining conventional and atypical antipsychotics.

Bold italics = treatment of choice

If little or no response to:	Preferred next step	Alternate next step
Conventional antipsychotic	***Switch to an atypical antipsychotic other than clozapine***	Switch to clozapine
Atypical antipsychotic	Switch to a different atypical antipsychotic other than clozapine	Switch to a conventional antipsychotic or clozapine

[27]Question 26

6F: Treatment-Refractory Bipolar Depression: When to Consider ECT[28]

ECT may be used at the beginning of treatment for patients who prefer it, for those who have psychotic depression (see Guideline 5A), or for those who are at risk for suicide or are medically compromised. Often, however, patients and clinicians prefer to begin with medications. The number of medication trials to undertake before switching to ECT depends on the severity of the illness. For severe psychotic depression, the experts recommend ECT as the treatment of choice for patients who have not responded to a trial of any single mood stabilizer and any 2 antidepressants. For severe nonpsychotic depression, the experts favor including lithium in the treatment regimen before proceeding to ECT. ECT may be a second-line option for patients with moderate bipolar depression who have failed to respond to trials of multiple mood stabilizers and multiple antidepressants.

Bold italics = treatment of choice

In the following situations	Consider ECT if little or no response to
Severe psychotic depression (assume the patient has also been receiving an antipsychotic)	***Any mood stabilizer plus 2 trials of antidepressants***
Severe nonpsychotic depression	***Lithium (with or without an anticonvulsant) plus 2 trials of antidepressants***
Moderate depression	Only after trials of at least 2 mood stabilizers and 2 antidepressants

[28]Question 27

6G: Other Approaches to Treatment-Refractory Bipolar Depression[29]

A wide range of treatments has been anecdotally reported to be helpful for treatment-refractory depression, whether unipolar or bipolar. We asked the experts to consider a range of these novel treatments for a patient who has failed to respond to numerous combinations of lithium, anticonvulsants, antidepressants, and thyroid hormone augmentation (assuming that rapid cycling, substance abuse, and psychosocial stress are not factors and that ECT is not an option).

No options were rated first-line. The higher second-line choices are light therapy for seasonal depression, atypical antipsychotics including clozapine, and stimulants as augmentation for patients who are already taking an antidepressant. As can be seen from the table, a number of other novel approaches might be considered second-line options. Among the options we asked about, St. John's wort and tiagabine received relatively low ratings, and phenytoin received the least support.

To use in combination with	High second-line	Other second-line
Mood stabilizer without antidepressant	Light therapy for seasonal depression Atypical antipsychotic including clozapine	Stimulant Dopamine agonist other than stimulant Omega-3 fatty acids Sleep deprivation Topiramate Nimodipine Inositol Buspirone Calcium channel blocker other than nimodipine Light therapy in nonseasonal depression
Mood stabilizer with antidepressant	Light therapy for seasonal depression Atypical antipsychotic including clozapine Stimulant	Dopamine agonist other than stimulant Pindolol augmentation Omega-3 fatty acids Buspirone Sleep deprivation Nimodipine Topiramate Inositol Calcium channel blocker other than nimodipine Light therapy in nonseasonal depression

[29]Question 29

III. TREATMENT OF RAPID-CYCLING BIPOLAR DISORDER

Guideline 7: Treatment of Rapid-Cycling Bipolar Disorder

7A. Overall Strategies for Rapid Cycling[30]

If a rapid-cycling patient has never previously been treated, the treatment of choice for either mania or depression is a single mood stabilizer. An alternative strategy would be to combine 2 mood stabilizers. Adding an atypical antipsychotic to the mood stabilizer regimen is a second-line option that is more highly rated for manic patients than depressed patients. Adding an antidepressant to the mood stabilizer is a second-line option for depressed patients but is to be avoided in manic patients.

For a manic patient who has not had an adequate response to a single mood stabilizer, the treatment of choice is to add a second mood stabilizer. Adding an atypical antipsychotic to the mood stabilizers is a first-line option.

If the patient is currently depressed while taking a mood stabilizer plus an antidepressant, the experts recommend replacing the antidepressant with a second mood stabilizer. Adding an atypical antipsychotic might also be considered. There was no consensus on the value of simply withdrawing the antidepressant or substituting a different antidepressant.

Presentation	Preferred strategies	Alternative strategies
Currently manic, never treated	***A single mood stabilizer***	Combine 2 mood stabilizers Combine mood stabilizer with an atypical antipsychotic
Currently manic, inadequate response to a single mood stabilizer	***Add a second mood stabilizer*** Combine mood stabilizer(s) with an atypical antipsychotic	
Currently depressed, never treated	***A single mood stabilizer***	Combine 2 mood stabilizers Combine mood stabilizer with an antidepressant Combine mood stabilizer with an atypical antipsychotic (lower second-line)
Currently depressed, inadequate response to a mood stabilizer + antidepressant	Add a second mood stabilizer, stop antidepressant	Add an atypical antipsychotic

Further recommendation for maintenance after depression: Clinicians face a dilemma in deciding how long to continue an apparently successful antidepressant in a patient with rapid cycling who has previously endured long episodes of depression despite multiple treatment trials with other regimens. No first-line consensus emerged from the expert panel. Some experts favor tapering the antidepressant in as little as 1 to 2 months, especially in bipolar I patients, while others recommend continuing the antidepressant for as long as 6 to 12 months, especially in bipolar II patients. However, the experts support a broad range of time periods, including indefinite treatment. The absence of consensus reflects the broad variation among patients with rapid cycling and hence the need to individualize this decision for each patient.[31]

[30]Question 30 [31]Question 31

7B. Choice of Mood Stabilizer for Monotherapy for Rapid Cycling[32]

Divalproex is the treatment of choice when using a mood stabilizer for monotherapy in a rapid-cycling patient in any type of episode. Lithium is a first-line choice for rapid-cycling patients with a current episode of depression, euphoric mania, or hypomania, and is a high second-line option for dysphoric or mixed mania. Lamotrigine is a first-line option for rapid-cycling patients who present with depression, and a second-line option for mania or hypomania. Carbamazepine is a first-line option for rapid-cycling patients who present with any type of mania and a high second-line option for those who present with an episode of depression or hypomania. Atypical antipsychotics are a second-line alternative for monotherapy, particularly for mania, and were generally ranked ahead of gabapentin. Monotherapy with a conventional antipsychotic is a third-line option for all types of rapid-cycling presentations.

Bold italics = treatment of choice

Clinical presentation	Preferred mood stabilizers	High second-line	Other second-line
Bipolar I, depressed	***Divalproex*** Lithium Lamotrigine	Carbamazepine	
Bipolar I, euphoric mania	***Divalproex*** Lithium Carbamazepine		Atypical antipsychotic Lamotrigine
Bipolar I, dysphoric or mixed mania	***Divalproex*** Carbamazepine	Lithium	Atypical antipsychotic Lamotrigine
Bipolar II, hypomania	***Divalproex*** Lithium	Carbamazepine	Lamotrigine

[32]Question 32

7C: Combining Mood Stabilizers for Breakthrough Mania in a Rapid-Cycling Patient[33]

If a patient with a history of rapid cycling appeared to be stable on a mood stabilizer and then experiences a breakthrough episode of mania, the experts recommend lithium or divalproex, if either is not already being used. Carbamazepine was also rated first-line. Lamotrigine is a highly rated second-line alternative, while there was less consensus about gabapentin.

Bold italics = treatment of choice

If patient is currently manic on	Preferred mood stabilizers to add	Alternative mood stabilizers to add
Carbamazepine	***Lithium*** Divalproex	Lamotrigine
Divalproex	***Lithium*** Carbamazepine	Lamotrigine
Lithium	***Divalproex*** Carbamazepine	Lamotrigine
Lithium + divalproex	Carbamazepine	Lamotrigine Gabapentin

[33]Question 33

7D: Strategies for Managing Recurrent Depression in a Rapid-Cycling Patient Who Cycles More Frequently on SSRIs[34]

A difficult problem in rapid-cycling depression is the "brittle" patient who, despite receiving a mood stabilizer, cycles up when given an antidepressant and quickly becomes depressed when the antidepressant is stopped. Because the SSRIs are the most widely used antidepressants, we first asked the experts to consider a patient who experiences this reaction to an SSRI plus lithium or divalproex. In this situation, the next step is to try a non-SSRI antidepressant. A highly rated alternative is to add a second mood stabilizer with or without an antidepressant of a different class. Adding thyroid hormone also deserves consideration. If the patient is already taking a combination of lithium and divalproex and still experiences this brittle reaction to an SSRI, trying a non-SSRI antidepressant is advised, with strong consideration given to adding a third antimanic drug. There is little support for merely lowering the dose of the mood stabilizer on the theory that a higher dose was somehow causing the depression.

If patient's current treatment regimen is	**Preferred strategies**	**Alternative strategies**
Lithium or divalproex monotherapy	Use a non-SSRI antidepressant *and/or* Add another antimanic medication*	Augment strategy with thyroid hormone *and/or* Add another antimanic drug and retry an SSRI
Lithium + divalproex	Use a non-SSRI antidepressant	Add another antimanic medication either alone or in combination with a non-SSRI antidepressant *and/or* Augment with thyroid hormone

*Rated very high second-line

[34]Question 34

7E: Strategies for Managing Recurrent Depression in a Rapid-Cycling Patient Who Cycles More Frequently With Any Antidepressant[35]

We asked the experts to recommend add-on treatment strategies for a patient with rapid-cycling bipolar I disorder who has frequent breakthrough episodes of depression despite complete adherence to maximal doses of a mood stabilizer regimen, and in whom a wide variety of antidepressants have led to manic or hypomanic episodes.

The preferred strategies are to ensure that the patient receives a trial of combined lithium and divalproex and to add lamotrigine if the patient is already receiving a combination of lithium and divalproex. Carbamazepine may also be combined with divalproex and lithium. Thyroid hormone and atypical antipsychotics are important back-up strategies. There was no consensus on using gabapentin as a second drug, although it is acceptable to add as a third drug to the combination of lithium and divalproex. Although some experts recommend ECT, there was no consensus on its place in the treatment algorithm in this situation.

Bold italics = treatment of choice

If patient's current mood stabilizer regimen is	Preferred treatments to add	High second-line	Other second-line
Divalproex	***Lithium*** Lamotrigine	Carbamazepine	Atypical antipsychotic Thyroid hormone
Lithium	Divalproex Lamotrigine Carbamazepine	Thyroid hormone	Atypical antipsychotic
Lithium + divalproex	Lamotrigine	Carbamazepine Thyroid hormone Atypical antipsychotic	Gabapentin
Carbamazepine	Lithium Divalproex Lamotrigine		Thyroid hormone Atypical antipsychotic

[35]Question 35

7F: Other Approaches for Rapid-Cycling Bipolar Disorder[36]

We asked the experts about a variety of alternative options as add-on treatment for a patient who continues to have rapid-cycling mania and depression despite treatment with various combinations of mood stabilizers, conventional and atypical antipsychotics other than clozapine, and benzodiazepines, and who has increased cycling on antidepressants. Thyroid hormone, light therapy for seasonal pattern episodes, and clozapine are preferred for depressive symptoms (although none were rated first-line). For manic symptoms, clozapine is rated first-line, while topiramate, thyroid hormone, and nimodipine are favored second-line strategies.

Type of symptomatology	**Preferred add-on treatments***	**Alternate add-on treatments**
Depressive symptoms	Thyroid hormone Light therapy for seasonal depression Clozapine	Dopamine agonist other than stimulant Sleep deprivation Omega-3 fatty acids Nimodipine Topiramate Inositol Buspirone Light therapy in nonseasonal depression Calcium channel blocker other than nimodipine
Manic symptoms	Clozapine (first-line) Topiramate	Thyroid hormone Nimodipine Omega-3 fatty acids Calcium channel blocker other than nimodipine Tiagabine

*Many experts commented on the importance of maintenance ECT for patients whose mania has been difficult to control with medication.

[36]Question 36

IV. OTHER TREATMENT ISSUES

Guideline 8: Selecting Medications for Bipolar Presentations That Resemble Other Disorders[37]

Many bipolar patients are misdiagnosed for a substantial period of time, often because their symptoms overlap with other disorders. Just as in straightforward cases, the preferred treatment is monotherapy with divalproex or lithium, with lithium being the treatment of choice for patients whose main problem is recurrent episodes of depression. Carbamazepine is a highly rated second-line option in all cases. Lamotrigine is also a highly rated second-line strategy for bipolar I patients with recurrent depression or for depressed bipolar II patients whose symptoms resemble borderline personality disorder. Adding an antidepressant is another option for depressed bipolar II patients. For bipolar I patients with prominent psychotic features, the addition of an antipsychotic to the mood stabilizer is recommended.

Bold italics = treatment of choice

Presentation	Previous diagnosis	New diagnosis	Preferred interventions	Alternative interventions
Yearly depressions, with some brief manic episodes (both spontaneous and antidepressant-triggered); euthymic intervals	Agitated unipolar depression	Bipolar I, recently depressed	***Lithium alone*** Divalproex alone	Carbamazepine alone Lamotrigine alone
Frequent psychotic manic episodes, some with mixed/dysphoric features; treated with antipsychotics; often demoralized and low-functioning; not psychotic when stable	Schizophrenia	Bipolar I, recently manic with psychotic features	Divalproex alone Lithium alone Include an antipsychotic in the initial plan*	Combine 2 top-ranked mood stabilizers Carbamazepine alone
Chronically depressed; occasional activated periods with increased energy and irritability; no sustained improvement on SSRIs	Borderline personality disorder + dysthymia	Bipolar II, recently depressed	Divalproex alone Lithium alone	Include an antidepressant in the initial plan Lamotrigine alone Carbamazepine alone
"Hyperactive" since childhood; sleeps little; some bouts of alcohol and marijuana abuse and minor sociopathy; brief but severe depressions with suicidality; agitated on stimulants	Attention-deficit/ hyperactivity disorder	Bipolar II, recently hypomanic	Divalproex alone Lithium alone	Carbamazepine alone Lamotrigine alone

*Received very high second-line rating, statistically indistinguishable from first-line options

[37]Question 37

Guideline 9: Use of Thyroid Hormone in Patients With Bipolar Disorder

9A: Strategies for Using Thyroid Hormone[38]

As shown in earlier guidelines (see Guidelines 6A, 6B, 7D, and 7E), the experts frequently consider including thyroid hormone among the options for improving response in refractory bipolar disorder. We asked the experts about how best to integrate thyroid augmentation in a variety of clinical situations, specifically when to combine thyroid hormone with both a mood stabilizer and an antidepressant and when to use it with a mood stabilizer alone. For patients with non–rapid-cycling bipolar disorder, thyroid hormone is most useful for augmenting an antidepressant plus mood stabilizer. In rapid-cycling patients whose main problem is frequent breakthrough depressions on antidepressants, thyroid may be helpful either to augment treatment with a mood stabilizer plus an antidepressant or may be added to the mood stabilizer alone. However, in the depressed rapid-cycling patient who switches to mania on antidepressants, the experts recommend adding thyroid hormone to the mood stabilizer alone.

Clinical presentation	**Preferred thyroid hormone strategies* (all patients are receiving mood stabilizers)**
Non–rapid-cycling bipolar disorder; inadequate response to antidepressant during acute episode	Combine thyroid hormone with antidepressant
Rapid cycling with frequent depressions despite continuous treatment with antidepressants; mania is suppressed on mood stabilizers	Use thyroid hormone either with or without an antidepressant
Rapid cycling in which patient is depressed on mood stabilizers alone but becomes manic or hypomanic when treated with antidepressants	Add thyroid hormone; avoid using an antidepressant

*No options received first-line ratings

[38]Question 38

9B: Duration of Thyroid Hormone Therapy[39]

	Length of initial trial to assess efficacy	**How long to continue before tapering if effective**
Non–rapid-cycling bipolar disorder	4–10 weeks	At least 4–9 months, 59% recommend continuing treatment indefinitely
Rapid-cycling bipolar disorder	4–11 weeks	At least 6–12 months, 75% recommend continuing treatment indefinitely

[39]Question 38

9C: Preferred Forms and Doses of Thyroid Hormone[40]

We asked the experts about the appropriateness of using T3 and T4 alone or in combination, and at replacement or hypermetabolic doses in 2 situations: 1) acute-phase augmentation of an antidepressant and 2) long-term management of rapid cycling.

Purpose	**Preferred forms and doses**	**Alternative forms and doses**
Acute-phase augmentation of an antidepressant	T3 at replacement dose*	T4 at replacement dose
Long-term management of rapid cycling	T4 at hypermetabolic or replacement doses	T3, or T3 + T4, at replacement doses

*Only option that received a first-line rating

[40]Question 39

9D: Monitoring Strategies During Long-Term Treatment With Hypermetabolic Doses of Thyroid Hormone[41]

While reportedly helpful for some patients, the long-term use of hypermetabolic doses of thyroid hormone* is controversial, especially because of concerns about possible effects on bone density.

In postmenopausal women, the experts favor periodically monitoring bone density as a guide to whether the dose of thyroid hormone should be reduced. Many experts also suggest bone density monitoring if there are clinical signs of hyperthyroidism. In other situations, there was little consensus on monitoring. In all cases, an alternative is simply to periodically attempt to reduce the dose of the thyroid hormone, without routinely monitoring bone density. The experts do not recommend continuing high dose thyroid hormone therapy indefinitely without some form of clinical or laboratory monitoring.

Clinical Situation	**Preferred strategies**	**Alternate strategies**
Clinically euthyroid, postmenopausal woman	Monitor bone density periodically[†]	Attempt dose reduction in the not too distant future—no need for routine bone density monitoring
Patient with mild signs of hyperthyroidism who is willing to tolerate these effects because of benefits to mood	Monitor bone density periodically *or* Attempt dose reduction in the not too distant future—no need for routine bone density monitoring	
Clinically euthyroid, not a postmenopausal woman	Attempt dose reduction in the not too distant future—no consensus on need for routine bone density monitoring	

*Hypermetabolic doses of thyroid hormone are often defined by suppression of thyroid stimulating hormone (TSH) to levels below its normal range or free T4 150% above the upper limit of normal.

[†]Only option that received a first-line rating

[41]Question 40

Guideline 10: Managing Special Problems

10A: Managing Weight Gain[42]

Weight gain is a problem for many patients receiving the first-line treatments for bipolar disorder: lithium, divalproex, or atypical antipsychotics.

For weight gain associated with mood stabilizers, the preference is to continue the present medication and attempt weight loss through diet or exercise. Adding topiramate or switching to a different mood stabilizer are second-line options; there was no consensus on whether dose reduction is helpful.

For weight gain associated with an atypical antispsychotic that has been dramatically helpful for a particular patient, the preference is to switch to another atypical antipsychotic or attempt dose reduction. Many experts also consider adding topiramate an option. Lowering the dose of a concomitantly administered mood stabilizer or switching to molindone are less likely to be helpful.

With either type of medication, there was only modest support for using appetite suppressants or thyroid hormone to induce weight loss.

Bold italics = treatment of choice

For weight gain associated with	Preferred strategies	High second-line alternatives	Other second-line alternatives
Lithium and/or divalproex: excellent clinical response but undesirable weight gain with long-term use	***Continue present medication and focus on diet and exercise***	Add topiramate	Switch to a different mood stabilizer (no consensus on whether a dose reduction would be helpful)
Atypical antipsychotic recently added to mood stabilizer: patient has had dramatic improvement but is steadily gaining weight despite diet and exercise	Intervene early by: Switching to another atypical antipsychotic* *or* Gradually decreasing the dose of the current atypical antipsychotic	Add topiramate	Decrease dose of mood stabilizer

*Ziprasidone was not available at the time of the survey, but experts who had used the drug in clinical trials felt that it might be helpful in this situation (see page 96).

[42]Questions 41 and 42

10B: Improving Adherence to Treatment[43]

The experts recommend a number of strategies for patients with a history of poor adherence to treatment.

Bold italics = treatment of choice

Preferred strategies	Alternate strategies
If on lithium or divalproex, use once-daily dosing ***Encourage use of adherence-enhancing aids (e.g., weekly pill boxes, daily mood charting)*** ***Enlist the help of family members to monitor or supervise medication use*** Close monitoring of medication blood levels	Incorporate use of a depot antipsychotic in the treatment regimen

[43]Question 43

10C: Selecting Medications for Patients With Comorbid Psychiatric or General Medical Conditions or Other Problems[44]

Clinicians must consider a variety of psychiatric, demographic, and medical issues in choosing among the agents that are often used to treat bipolar disorder. We asked the experts about the general safety and desirability of using the following medications in a variety of circumstances: carbamazepine, divalproex, gabapentin, lamotrigine, lithium, atypical antipsychotics, and conventional antipsychotics. In the following table, we show preferred and highly rated second-line options, as well as medications that are more problematic in certain situations. Medications from the list that do not appear in the table are acceptable second-line alternatives in that situation.

Bold italics = treatment of choice

Prominent features of the episode

Clinical presentation	Preferred first-line	Highly rated second-line	Not generally recommended (3rd-line)
Marked insomnia	Divalproex Atypical antipsychotic	Carbamazepine Gabapentin Lithium Conventional antipsychotic	
Marked psychomotor agitation	Divalproex Atypical antipsychotic	Carbamazepine Lithium Conventional antipsychotic Gabapentin	
Marked psychomotor retardation	Lithium	Lamotrigine Divalproex Carbamazepine	
Marked aggression/ violence	***Divalproex*** Atypical antipsychotic Carbamazepine Lithium	Conventional antipsychotic	

Comorbid psychiatric conditions

Clinical presentation	Preferred first-line	Highly rated second-line	Not generally recommended (3rd-line)
Panic disorder	Divalproex Gabapentin	Carbamazepine Lithium	Conventional antipsychotic
Obsessive-compulsive disorder	*No consensus on preferred choices*	Divalproex Lithium	
Attention-deficit/ hyperactivity disorder	*No consensus on preferred choices*	Divalproex Lithium	Conventional antipsychotic
Posttraumatic stress disorder	Divalproex	Carbamazepine Gabapentin Lithium	
Bulimia nervosa	*No first-line options*	Divalproex	Conventional antipsychotic
Alcohol abuse	Divalproex Lithium*	Atypical antipsychotic Gabapentin Carbamazepine	
Other substance abuse	Divalproex	Carbamazepine Lithium Atypical antipsychotic Gabapentin	

Comorbid general medical problems

Clinical presentation	Preferred first-line	Highly rated second-line	Not generally recommended (3rd-line)
Renal insufficiency	Divalproex Atypical antipsychotic Carbamazepine	Lamotrigine Conventional antipsychotic	Lithium
Liver disease	***Lithium***	Gabapentin	Carbamazepine Divalproex
Heart disease	Divalproex	Gabapentin Atypical antipsychotic Lamotrigine Lithium	
Stroke or head injury resulting in mania	***Divalproex*** Carbamazepine	Atypical antipsychotic	
Patient concerned about gaining weight	Carbamazepine* Lamotrigine*	Gabapentin	

Reproductive issues

Clinical presentation	Preferred first-line	Highly rated second-line	Not generally recommended (3rd-line)
Young woman wishing to become pregnant	*No consensus on preferred choices*		Carbamazepine Divalproex
Trying to get pregnant and needing medication	Conventional antipsychotic*	Atypical antipsychotic	Carbamazepine Divalproex
First trimester of pregnancy and needing medication	Conventional antipsychotic*	Atypical antipsychotic	Gabapentin Lamotrigine Carbamazepine Divalproex
Second–third trimester of pregnancy and needing medication	Lithium* Conventional or atypical antipsychotic*		
Postpartum, breast-feeding, and needing medication	*No consensus on preferred choices*		

Age-related issues

Clinical presentation	Preferred first-line	Highly rated second-line	Not generally recommended (3rd-line)
Prepubertal child	Lithium	Divalproex	Conventional antipsychotic
Adolescent girl	Lithium	Carbamazepine Divalproex	Conventional antispychotic
Adolescent boy	Divalproex Lithium	Carbamazepine	Conventional antipsychotic
Elderly patient with dementia	Divalproex Atypical antipsychotic	Carbamazepine	

*Very high second-line

[44]Questions 44–46

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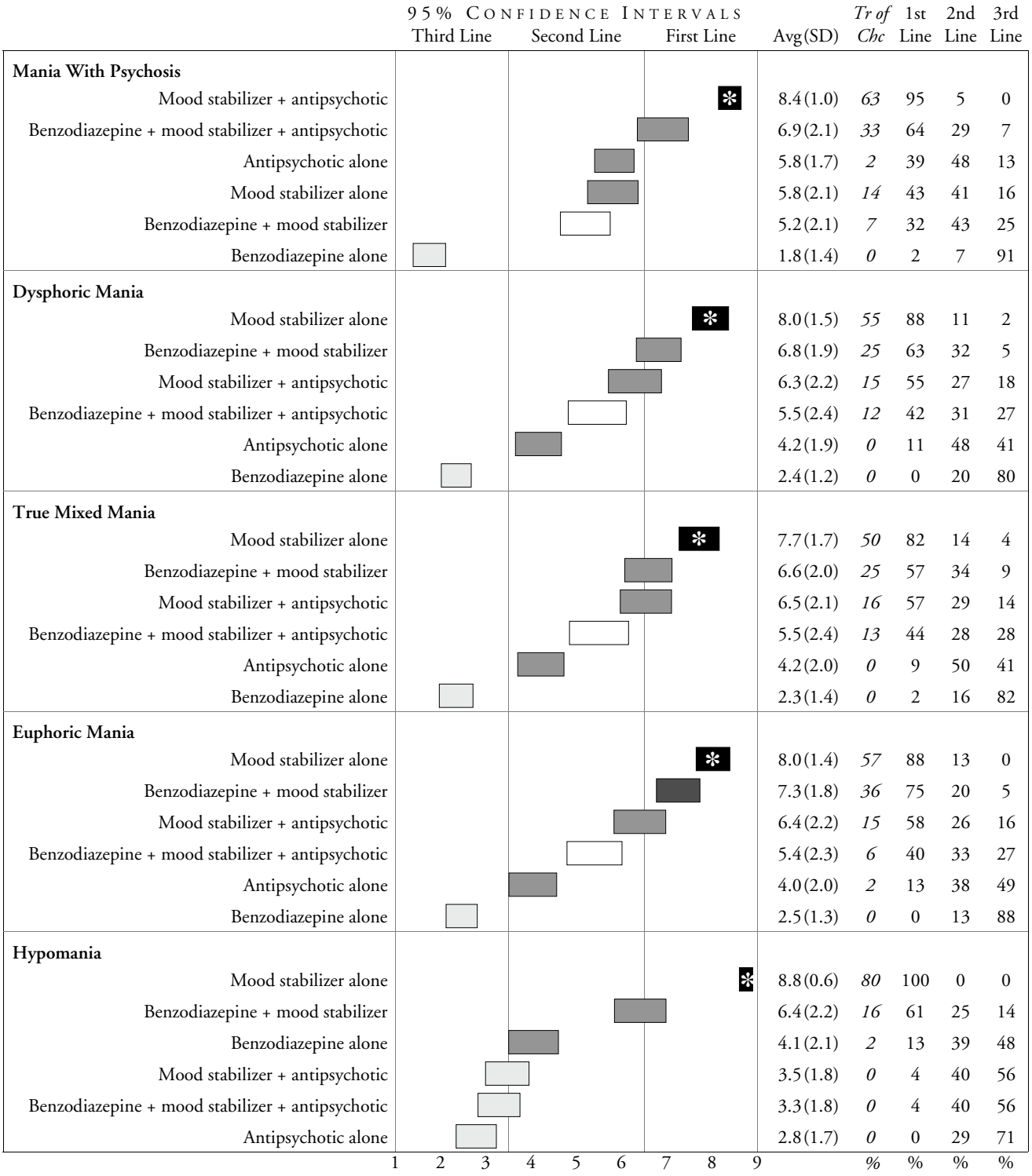
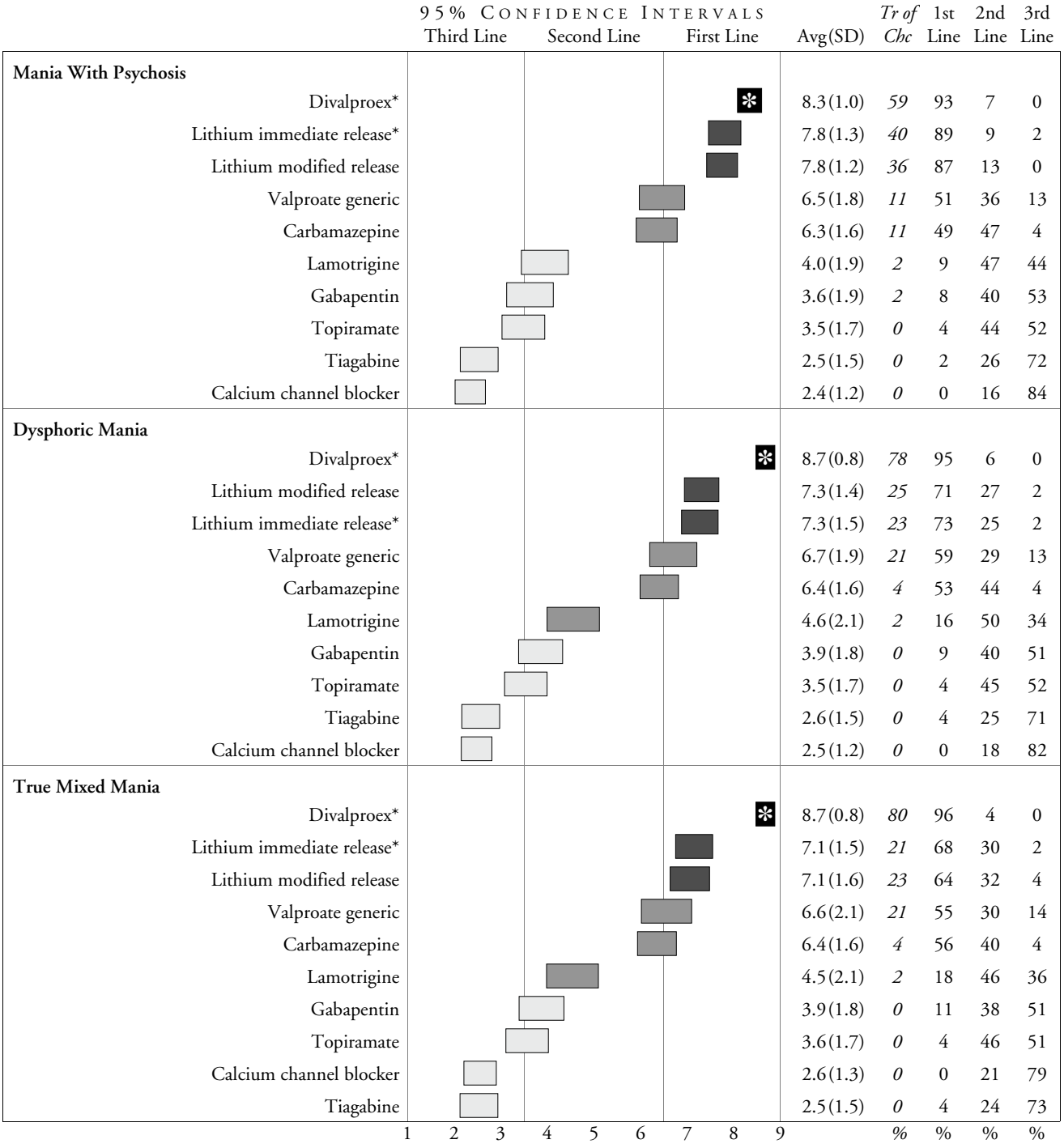
Expert Survey Results and Guideline References

1 **Treatment of mania: first episode, initial strategy**. A physically healthy person in his or her 20s presents with a first manic episode severe enough to warrant hospital admission, or a first hypomanic episode severe enough to pose a likely eventual threat to functioning if unchecked. Based on the dominant symptom pictures shown below, please rate each of the following overall strategies as an initial intervention, assuming the patient is willing to take oral medication. (Subsequent questions will ask you about specific medications within the broad classes.)



	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mania With Psychosis					
Mood stabilizer + antipsychotic	8.4 (1.0)	*63*	95	5	0
Benzodiazepine + mood stabilizer + antipsychotic	6.9 (2.1)	*33*	64	29	7
Antipsychotic alone	5.8 (1.7)	*2*	39	48	13
Mood stabilizer alone	5.8 (2.1)	*14*	43	41	16
Benzodiazepine + mood stabilizer	5.2 (2.1)	*7*	32	43	25
Benzodiazepine alone	1.8 (1.4)	*0*	2	7	91
Dysphoric Mania					
Mood stabilizer alone	8.0 (1.5)	*55*	88	11	2
Benzodiazepine + mood stabilizer	6.8 (1.9)	*25*	63	32	5
Mood stabilizer + antipsychotic	6.3 (2.2)	*15*	55	27	18
Benzodiazepine + mood stabilizer + antipsychotic	5.5 (2.4)	*12*	42	31	27
Antipsychotic alone	4.2 (1.9)	*0*	11	48	41
Benzodiazepine alone	2.4 (1.2)	*0*	0	20	80
True Mixed Mania					
Mood stabilizer alone	7.7 (1.7)	*50*	82	14	4
Benzodiazepine + mood stabilizer	6.6 (2.0)	*25*	57	34	9
Mood stabilizer + antipsychotic	6.5 (2.1)	*16*	57	29	14
Benzodiazepine + mood stabilizer + antipsychotic	5.5 (2.4)	*13*	44	28	28
Antipsychotic alone	4.2 (2.0)	*0*	9	50	41
Benzodiazepine alone	2.3 (1.4)	*0*	2	16	82
Euphoric Mania					
Mood stabilizer alone	8.0 (1.4)	*57*	88	13	0
Benzodiazepine + mood stabilizer	7.3 (1.8)	*36*	75	20	5
Mood stabilizer + antipsychotic	6.4 (2.2)	*15*	58	26	16
Benzodiazepine + mood stabilizer + antipsychotic	5.4 (2.3)	*6*	40	33	27
Antipsychotic alone	4.0 (2.0)	*2*	13	38	49
Benzodiazepine alone	2.5 (1.3)	*0*	0	13	88
Hypomania					
Mood stabilizer alone	8.8 (0.6)	*80*	100	0	0
Benzodiazepine + mood stabilizer	6.4 (2.2)	*16*	61	25	14
Benzodiazepine alone	4.1 (2.1)	*2*	13	39	48
Mood stabilizer + antipsychotic	3.5 (1.8)	*0*	4	40	56
Benzodiazepine + mood stabilizer + antipsychotic	3.3 (1.8)	*0*	4	40	56
Antipsychotic alone	2.8 (1.7)	*0*	0	29	71
		%	%	%	%

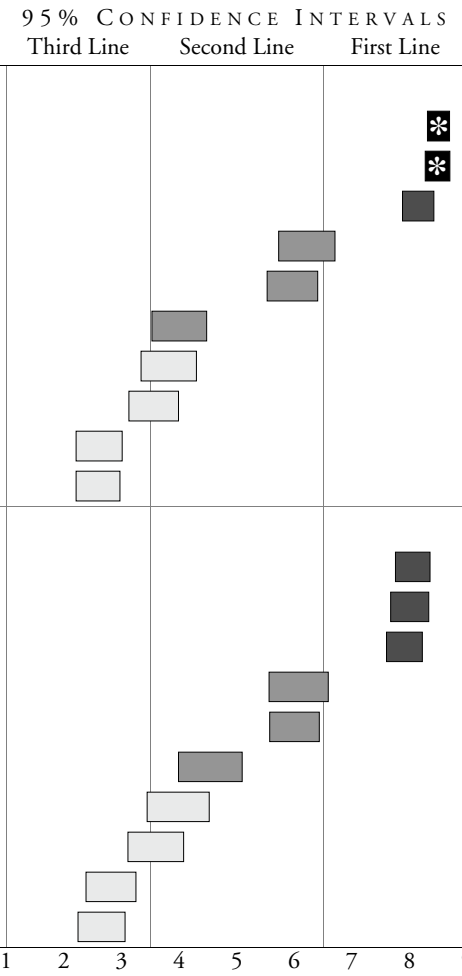
2 **Treatment of mania: first episode, choice of mood stabilizer.** In the situation described in question 1, assume you have decided to use a mood stabilizer as part of your treatment plan. A number of medications have been established as or suggested to be mood stabilizers. Please rate each of the following as an initial choice in each of the symptom presentations.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mania With Psychosis					
Divalproex*	8.3(1.0)	*59*	93	7	0
Lithium immediate release*	7.8(1.3)	*40*	89	9	2
Lithium modified release	7.8(1.2)	*36*	87	13	0
Valproate generic	6.5(1.8)	*11*	51	36	13
Carbamazepine	6.3(1.6)	*11*	49	47	4
Lamotrigine	4.0(1.9)	*2*	9	47	44
Gabapentin	3.6(1.9)	*2*	8	40	53
Topiramate	3.5(1.7)	*0*	4	44	52
Tiagabine	2.5(1.5)	*0*	2	26	72
Calcium channel blocker	2.4(1.2)	*0*	0	16	84
Dysphoric Mania					
Divalproex*	8.7(0.8)	*78*	95	6	0
Lithium modified release	7.3(1.4)	*25*	71	27	2
Lithium immediate release*	7.3(1.5)	*23*	73	25	2
Valproate generic	6.7(1.9)	*21*	59	29	13
Carbamazepine	6.4(1.6)	*4*	53	44	4
Lamotrigine	4.6(2.1)	*2*	16	50	34
Gabapentin	3.9(1.8)	*0*	9	40	51
Topiramate	3.5(1.7)	*0*	4	45	52
Tiagabine	2.6(1.5)	*0*	4	25	71
Calcium channel blocker	2.5(1.2)	*0*	0	18	82
True Mixed Mania					
Divalproex*	8.7(0.8)	*80*	96	4	0
Lithium immediate release*	7.1(1.5)	*21*	68	30	2
Lithium modified release	7.1(1.6)	*23*	64	32	4
Valproate generic	6.6(2.1)	*21*	55	30	14
Carbamazepine	6.4(1.6)	*4*	56	40	4
Lamotrigine	4.5(2.1)	*2*	18	46	36
Gabapentin	3.9(1.8)	*0*	11	38	51
Topiramate	3.6(1.7)	*0*	4	46	51
Calcium channel blocker	2.6(1.3)	*0*	0	21	79
Tiagabine	2.5(1.5)	*0*	4	24	73
		%	%	%	%

*Divalproex > lithium, $P<0.003$

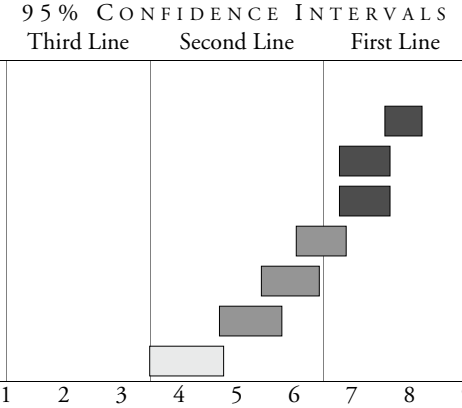
2 **Treatment of mania: first episode, choice of mood stabilizer, *continued***



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Euphoric Mania					
Lithium immediate release†	8.5(0.7)	*63*	100	0	0
Lithium modified release	8.5(0.8)	*64*	96	4	0
Divalproex†	8.2(1.0)	*49*	93	7	0
Valproate generic	6.2(1.9)	*9*	48	38	14
Carbamazepine	6.0(1.6)	*6*	38	56	6
Lamotrigine	4.0(1.8)	*2*	4	57	39
Gabapentin	3.8(1.8)	*0*	9	40	51
Topiramate	3.6(1.6)	*0*	2	52	46
Tiagabine	2.6(1.5)	*0*	2	25	73
Calcium channel blocker	2.6(1.4)	*0*	4	14	82
Hypomania					
Lithium immediate release†	8.1(1.1)	*47*	91	9	0
Divalproex†	8.0(1.2)	*48*	91	9	0
Lithium modified release	7.9(1.2)	*44*	89	11	0
Valproate generic	6.1(1.9)	*11*	44	38	18
Carbamazepine	6.0(1.6)	*9*	36	57	8
Gabapentin	4.5(2.1)	*6*	15	50	35
Lamotrigine	4.0(2.0)	*0*	11	44	46
Topiramate	3.6(1.8)	*0*	4	50	46
Calcium channel blocker	2.8(1.6)	*0*	4	28	69
Tiagabine	2.7(1.5)	*0*	2	26	72
		%	%	%	%

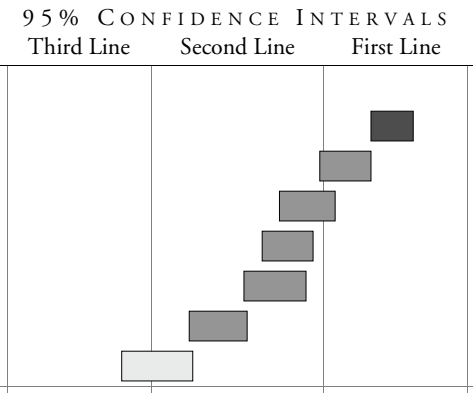
†Not significant, criterion for significance adjusted for multiple comparisons

3 **Treatment of mania: first episode, choice of antipsychotic.** In the situation described in question 1, assume you have decided to use an oral antipsychotic as part of your initial treatment plan. Please rate each of the following as an initial choice in each of the symptom presentations.*



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mania With Psychosis					
Olanzapine	7.9(1.2)	*36*	87	13	0
High-potency conventional antipsychotic	7.2(1.6)	*27*	73	26	2
Risperidone	7.2(1.7)	*24*	71	27	2
Mid-potency conventional antipsychotic	6.5(1.6)	*9*	50	46	4
Quetiapine	5.9(1.9)	*7*	39	52	9
Low-potency conventional antipsychotic	5.2(2.0)	*4*	27	51	22
Combined conventional and atypical antipsychotics	4.1(2.4)	*7*	16	38	46
		%	%	%	%

3 **Treatment of mania: first episode, choice of antipsychotic, *continued***



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Dysphoric Mania					
Olanzapine	7.7(1.4)	*42*	79	21	0
Risperidone	6.9(1.6)	*17*	64	34	2
High-potency conventional antipsychotic	6.2(1.8)	*13*	40	55	6
Mid-potency conventional antipsychotic	5.9(1.6)	*6*	33	62	6
Quetiapine	5.7(2.0)	*8*	33	55	12
Low-potency conventional antipsychotic	4.7(1.9)	*2*	17	57	26
Combined conventional and atypical antipsychotics	3.6(2.3)	*6*	11	32	57
True Mixed Mania					
Olanzapine	7.7(1.4)	*40*	84	15	2
Risperidone	6.8(1.7)	*16*	62	35	4
High-potency conventional antipsychotic	6.2(1.8)	*13*	42	53	6
Mid-potency conventional antipsychotic	5.9(1.6)	*6*	32	63	6
Quetiapine	5.8(1.9)	*9*	35	54	11
Low-potency conventional antipsychotic	4.8(1.9)	*2*	22	51	27
Combined conventional and atypical antipsychotics	3.6(2.2)	*4*	9	36	55
Euphoric Mania					
Olanzapine	7.6(1.3)	*35*	82	18	0
Risperidone	6.9(1.6)	*16*	66	33	2
High-potency conventional antipsychotic	6.4(1.8)	*13*	47	47	6
Mid-potency conventional antipsychotic	6.1(1.8)	*7*	37	57	6
Quetiapine	5.7(1.9)	*7*	35	54	11
Low-potency conventional antipsychotic	4.9(2.0)	*4*	22	47	31
Combined conventional and atypical antipsychotics	3.6(2.2)	*6*	9	36	55
Hypomania					
Olanzapine	6.5(2.6)	*33*	60	26	15
Risperidone	6.1(2.5)	*20*	55	31	15
Quetiapine	5.1(2.4)	*9*	28	46	26
Mid-potency conventional antipsychotic	4.8(2.4)	*6*	24	41	35
High-potency conventional antipsychotic	4.5(2.4)	*6*	22	38	40
Low-potency conventional antipsychotic	3.8(2.2)	*2*	9	40	51
Combined conventional and atypical antipsychotics	2.6(2.0)	*0*	9	15	76
		%	%	%	%

*Overall 2-factor ANOVA showed significant effect for available atypical antipsychotics (olanzapine, risperidone, quetiapine) over conventional antipsychotics; F = 122.987, *P* = 0.000

4 **Inadequate response to initial mood stabilizer: adding a second.** Suppose your initial strategy included a mood stabilizer and that, despite adding various antipsychotics and a benzodiazepine, the patient exhibits only a partial response. In a previous survey, experts suggested adding a second mood stabilizer within 1 to 3 weeks if there has been no response to the first, or within 2 to 4 weeks if there has been a partial response. Assuming the initial mood stabilizer has been used for at least 2 weeks at the highest tolerable dose, please rate each of the following as your next choice to add on to each of the initial treatments shown below.

Initial Mood Stabilizer Was:	95% Confidence Intervals: Third Line / Second Line / First Line	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Divalproex						
Lithium		8.7 (0.7)	*84*	98	2	0
Carbamazepine		6.2 (1.6)	*2*	46	49	6
Gabapentin		5.3 (1.8)	*4*	34	46	20
Lamotrigine		4.8 (1.8)	*0*	20	52	29
Lithium						
Divalproex		8.8 (0.6)	*84*	98	2	0
Carbamazepine		7.2 (1.3)	*20*	70	30	0
Gabapentin		5.5 (2.1)	*13*	32	50	18
Lamotrigine		5.5 (1.8)	*4*	35	51	15
Carbamazepine						
Lithium		8.7 (0.6)	*77*	100	0	0
Divalproex		7.2 (1.8)	*27*	73	23	4
Gabapentin		5.1 (1.8)	*2*	27	51	22
Lamotrigine		4.9 (1.8)	*2*	24	51	26
Lamotrigine						
Lithium		8.5 (1.2)	*78*	93	7	0
Divalproex		6.6 (2.3)	*26*	61	24	15
Carbamazepine		5.5 (1.9)	*4*	33	54	14
Gabapentin		4.8 (1.8)	*2*	20	54	26
Gabapentin						
Lithium		8.6 (0.8)	*75*	98	2	0
Divalproex		8.0 (1.5)	*55*	89	9	2
Carbamazepine		6.4 (1.6)	*11*	49	45	6
Lamotrigine		4.8 (1.7)	*0*	13	64	24
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

5 **Antipsychotic treatment of mania: duration of trial.** Assume you have been prescribing an antipsychotic along with the initial mood stabilizer in order to treat either psychosis or agitation, but that the patient is not responding adequately. How long would you wait, from the time you first began the medication, before changing to another antipsychotic? (Assume the patient is not experiencing extrapyramidal side effects, or that these have been adequately treated. Also assume you have been giving a benzodiazepine at the maximum appropriate dose.)

	Minimum days Avg (SD)	Maximum days Avg (SD)
Partial response to atypical	9.19 (7.1)	19.04 (15.7)
Partial response to conventional	8.04 (5.5)	17.09 (11.7)
Little or no response atypical	5.48 (3.5)	10.81 (6.2)
Little or no response to conventional	4.83 (3.3)	9.80 (5.8)

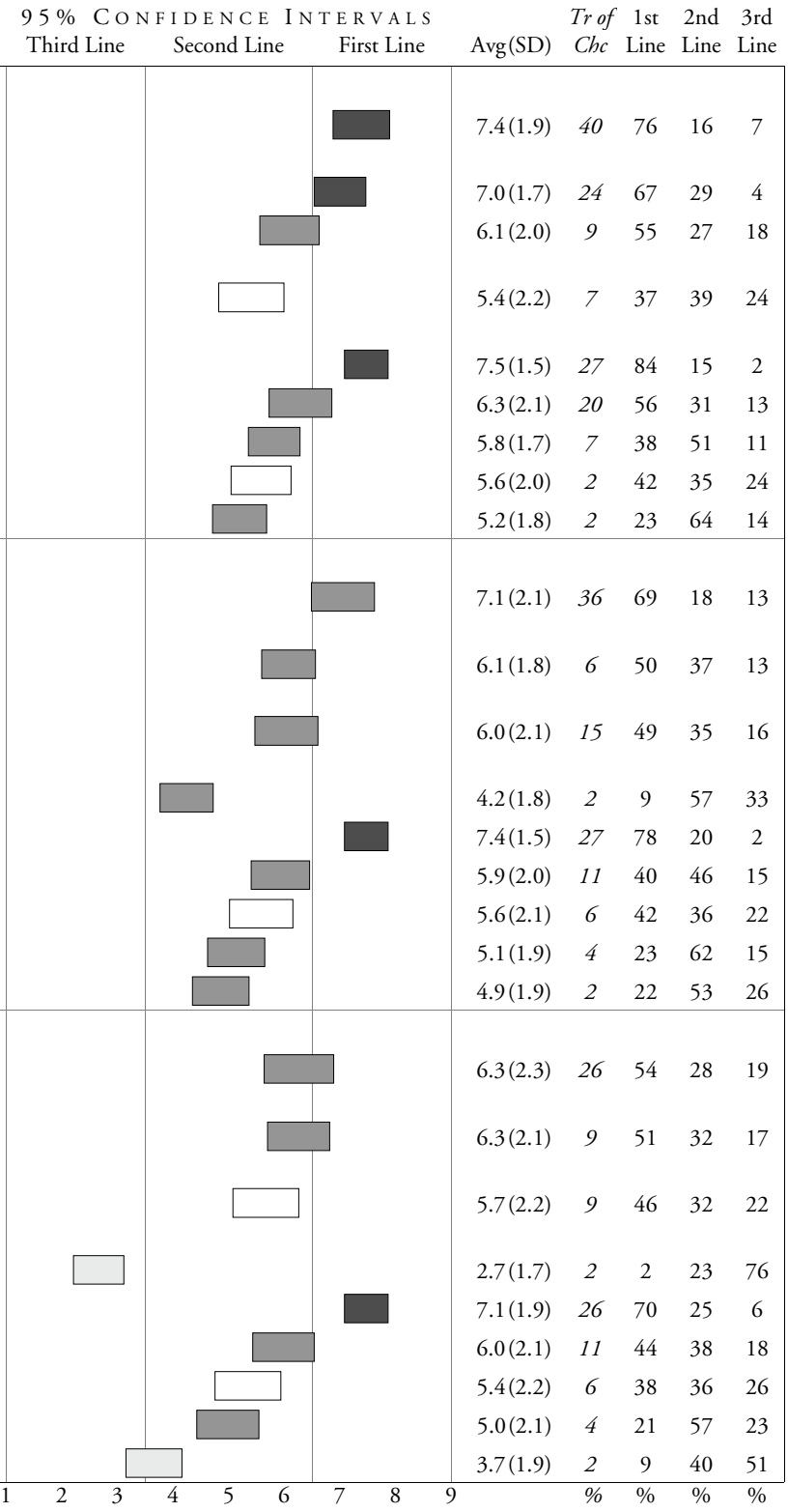
6 **Inadequate response to initial antipsychotic for mania: switching to a second.** In the situation described in question 5, please rate the following strategies for picking the next antipsychotic if your initial choice has not produced an adequate response after an appropriate dose and duration. Would you pick another drug in the same class, switch to the other class, or combine classes?

Initial Class Was:	95% Confidence Intervals	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
	Third Line / Second Line / First Line					
Conventional Antipsychotic						
Atypical antipsychotic		7.8(1.4)	*43*	85	11	4
Combine atypical with conventional antipsychotic		5.8(2.3)	*17*	41	39	20
Conventional antipsychotic		5.4(2.2)	*6*	37	35	28
Atypical Antipsychotic						
Conventional antipsychotic		7.3(1.7)	*28*	77	17	6
Atypical antipsychotic		7.0(1.8)	*26*	69	28	4
Combine atypical with conventional antipsychotic		5.8(2.3)	*17*	39	43	19
1 2 3 4 5 6 7 8 9			%	%	%	%

7 **Continued treatment resistance in first episode of mania: inadequate response to combined lithium and divalproex.** Assume a patient with an initial manic episode still has symptoms after 4 to 6 weeks of mood stabilizer treatment including 2 to 3 weeks of combined lithium + divalproex. The patient has also received a benzodiazepine and trials of both conventional and atypical antipsychotics. Doses are the maximum tolerable. Please rate each of the following options for strategies and specific interventions, depending on the degree of remaining symptoms (from severe to mild).

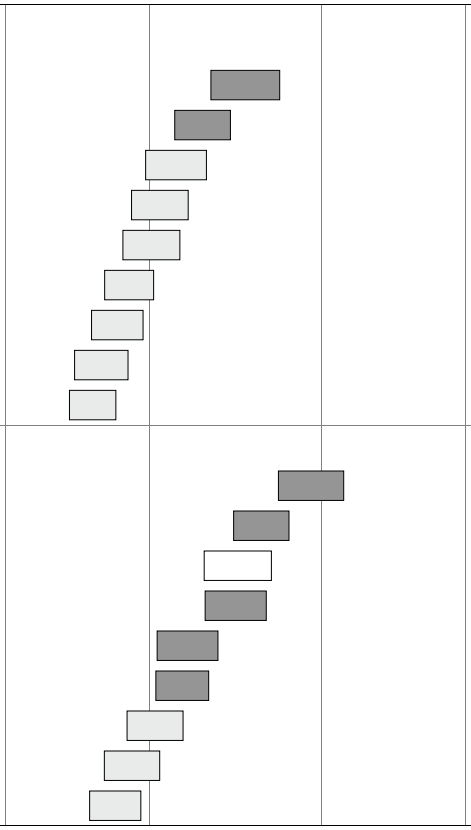
Present Status Is:	95% Confidence Intervals	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
	Third Line / Second Line / First Line					
Mania With Psychosis						
Switch to ECT		7.5(1.7)	*38*	75	23	2
Continue present medication and add another antimanic medication		7.1(2.0)	*34*	68	23	9
Taper and stop lithium and/or divalproex and add another antimanic medication		5.9(1.9)	*5*	46	34	20
Taper and stop antipsychotic and/or benzodiazepine and add another antimanic medication		4.6(2.3)	*4*	26	40	35
If using another medication, options for next step:						
Carbamazepine		7.1(1.6)	*23*	75	21	4
Clozapine		7.0(1.8)	*34*	63	34	4
Gabapentin		5.6(1.9)	*7*	34	48	18
Lamotrigine		5.4(2.0)	*2*	36	39	25
Other antimanic medication not listed above		5.0(1.8)	*2*	19	65	17
1 2 3 4 5 6 7 8 9			%	%	%	%

7 **Continued treatment resistance in first episode of mania: inadequate response to combined lithium and divalproex, *continued***



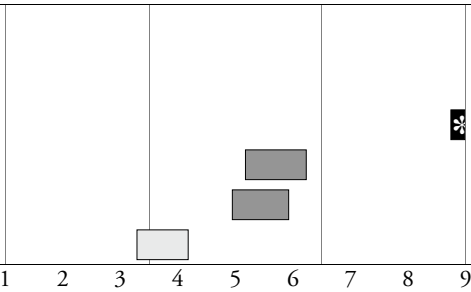
Present Status Is:		Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mania, Not Psychotic						
Continue present medication and add another antimanic medication		7.4 (1.9)	*40*	76	16	7
Switch to ECT		7.0 (1.7)	*24*	67	29	4
Taper and stop lithium and/or divalproex and add another antimanic medication		6.1 (2.0)	*9*	55	27	18
Taper and stop antipsychotic and/or benzodiazepine and add another antimanic medication		5.4 (2.2)	*7*	37	39	24
If using another medication:	Carbamazepine	7.5 (1.5)	*27*	84	15	2
	Clozapine	6.3 (2.1)	*20*	56	31	13
	Gabapentin	5.8 (1.7)	*7*	38	51	11
	Lamotrigine	5.6 (2.0)	*2*	42	35	24
	Other antimanic medication not listed above	5.2 (1.8)	*2*	23	64	14
Moderate Residual Symptoms						
Continue present medication and add another antimanic medication		7.1 (2.1)	*36*	69	18	13
Taper and stop antipsychotic and/or benzodiazepine and add another antimanic medication		6.1 (1.8)	*6*	50	37	13
Taper and stop lithium and/or divalproex and add another antimanic medication		6.0 (2.1)	*15*	49	35	16
Switch to ECT		4.2 (1.8)	*2*	9	57	33
If using another medication:	Carbamazepine	7.4 (1.5)	*27*	78	20	2
	Gabapentin	5.9 (2.0)	*11*	40	46	15
	Lamotrigine	5.6 (2.1)	*6*	42	36	22
	Other antimanic medication not listed above	5.1 (1.9)	*4*	23	62	15
	Clozapine	4.9 (1.9)	*2*	22	53	26
Mild Residual Symptoms						
Continue present medication and add another antimanic medication		6.3 (2.3)	*26*	54	28	19
Taper and stop antipsychotic and/or benzodiazepine and add another antimanic medication		6.3 (2.1)	*9*	51	32	17
Taper and stop lithium and/or divalproex and add another antimanic medication		5.7 (2.2)	*9*	46	32	22
Switch to ECT		2.7 (1.7)	*2*	2	23	76
If using another medication:	Carbamazepine	7.1 (1.9)	*26*	70	25	6
	Gabapentin	6.0 (2.1)	*11*	44	38	18
	Lamotrigine	5.4 (2.2)	*6*	38	36	26
	Other antimanic medication not listed above	5.0 (2.1)	*4*	21	57	23
	Clozapine	3.7 (1.9)	*2*	9	40	51
			%	%	%	%

8 **Novel approaches to treatment-resistant mania.** Suppose you have tried several combinations of the "mainstream" mood stabilizers offered as options in the previous question at adequate doses for sufficient periods of time without success. Please rate each of the following alternatives as options to add on or cautiously substitute.



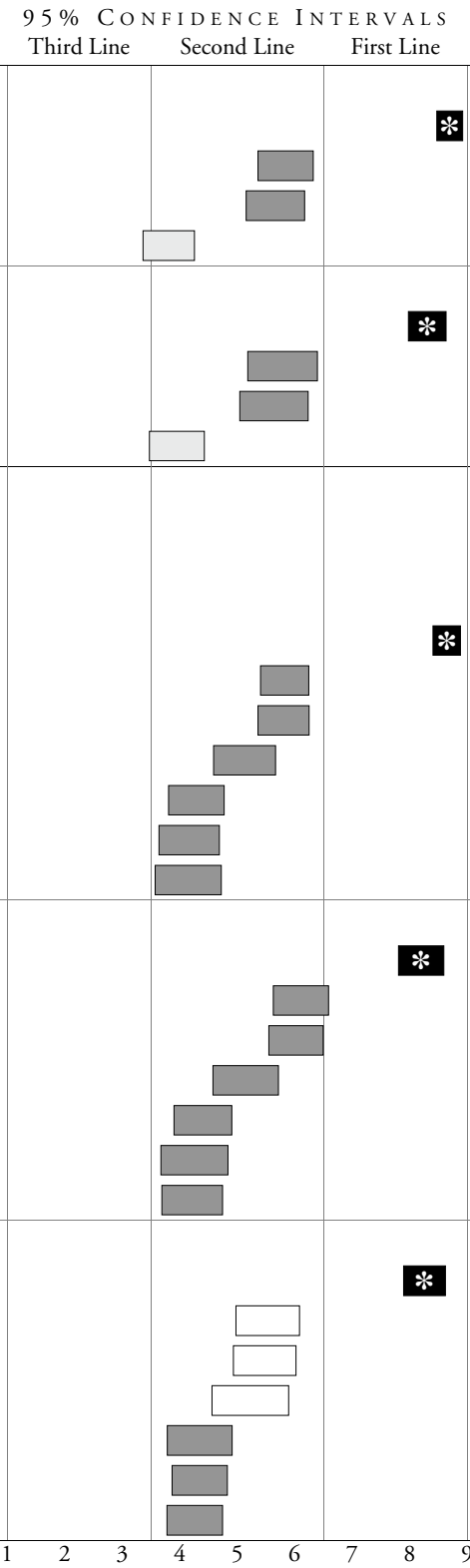
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
As Monotherapy With Adjunctive Antipsychotics or Benzodiazepines					
Topiramate	5.2(2.2)	*9*	26	56	19
Nimodipine	4.4(1.8)	*4*	9	59	32
Calcium channel blocker other than nimodipine	4.0(2.0)	*2*	11	43	46
Omega-3 fatty acids	3.7(1.8)	*0*	7	46	46
Tiagabine	3.5(1.9)	*0*	7	43	50
Adrenergic antagonist	3.2(1.6)	*0*	2	35	63
Cholinesterase inhibitor	2.9(1.7)	*0*	2	37	61
Tamoxifen	2.7(1.7)	*2*	4	24	72
Phenytoin	2.5(1.5)	*0*	2	17	82
As an Add-On to Another Mood Stabilizer					
Topiramate	6.3(2.1)	*16*	56	35	9
Nimodipine	5.4(1.8)	*4*	28	57	15
Omega-3 fatty acids	5.0(2.2)	*6*	26	47	27
Calcium channel blocker other than nimodipine	5.0(2.0)	*4*	22	53	26
Tiagabine	4.2(2.0)	*0*	15	49	36
Adrenergic antagonist	4.1(1.7)	*0*	7	51	42
Cholinesterase inhibitor	3.6(1.8)	*0*	7	46	47
Tamoxifen	3.2(1.8)	*2*	6	35	60
Phenytoin	2.9(1.7)	*0*	6	24	71
		%	%	%	%

9 **Long-term maintenance after a manic episode.** A previous survey found that long-term or lifetime prophylaxis was recommended for patients who had had 2 or more manic episodes. We now ask you to rate long-term strategies after a second manic episode. Assume a patient recovers from an initial episode on 1 of the mood stabilizer regimens specified below. The medication is eventually tapered off and, 1 year after stopping medication, a second episode occurs, which again responds to the same regimen as the first episode. Now you must decide on a choice for long-term maintenance. Please consider 3 common situations, based on past history of depression as shown in the life charts.



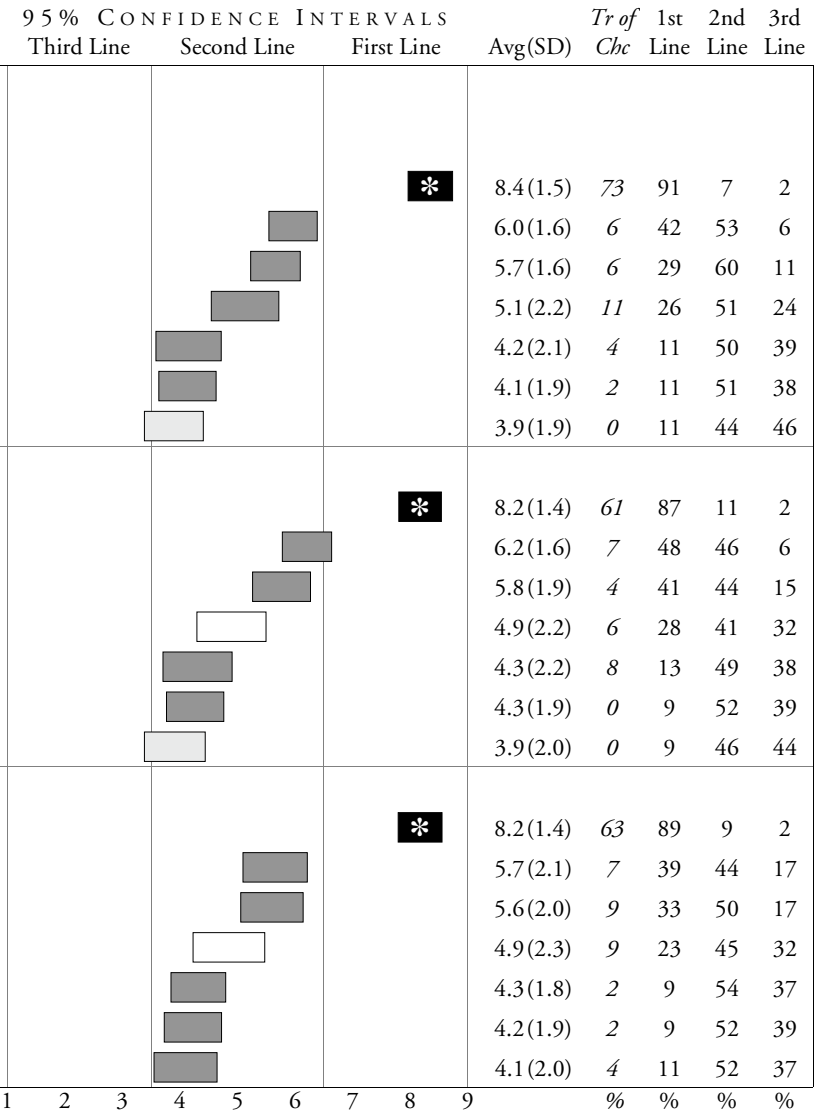
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
SITUATION 1: Following remission of second manic episode; no prior depressions					
1a. Acute phase regimen was lithium alone					
Lithium monotherapy	8.9(0.4)	*89*	100	0	0
Divalproex monotherapy	5.7(2.0)	*5*	38	50	13
Combined lithium + divalproex	5.4(1.9)	*4*	30	52	18
Add or substitute another putative mood stabilizer	3.7(1.7)	*0*	0	57	43
		%	%	%	%

9 Long-term maintenance after a manic episode, *continued*



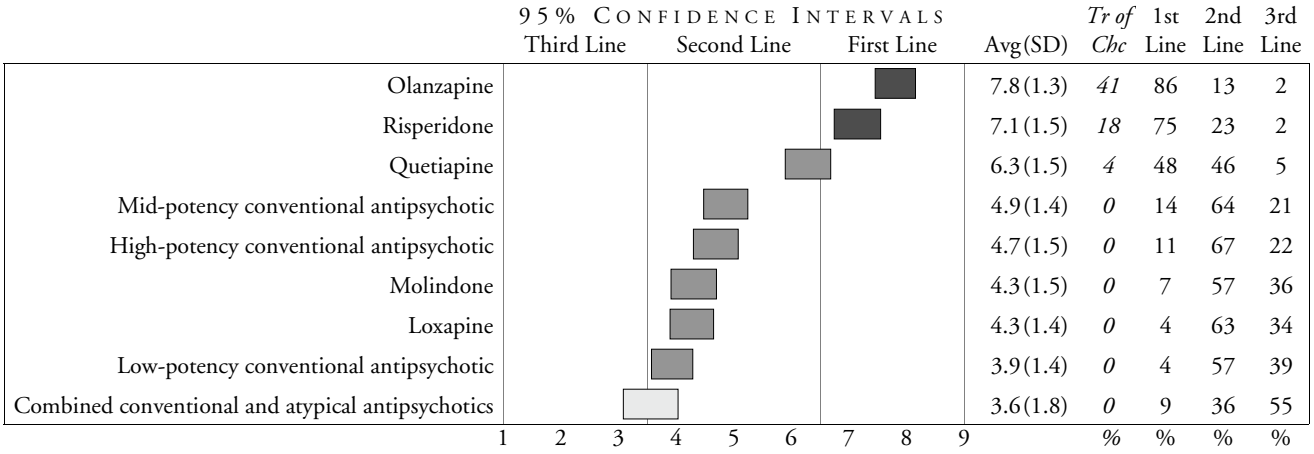
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
1b. Acute phase regimen was divalproex alone					
Divalproex monotherapy	8.7(0.9)	*82*	96	4	0
Lithium monotherapy	5.8(1.8)	*5*	39	46	14
Combined lithium + divalproex	5.7(1.9)	*5*	34	52	14
Add or substitute another putative mood stabilizer	3.8(1.7)	*0*	2	57	41
1c. Acute phase regimen was lithium + divalproex					
Combined lithium + divalproex	8.3(1.2)	*64*	91	9	0
Lithium monotherapy	5.8(2.3)	*14*	39	41	20
Divalproex monotherapy	5.6(2.2)	*9*	38	42	20
Add or substitute another putative mood stabilizer	4.0(1.8)	*2*	7	52	41
SITUATION 2: History of severe depressions responsive to antidepressant; first manic episode precipitated by antidepressant without mood stabilizer					
2a. Acute phase regimen was lithium alone					
Lithium monotherapy	8.6(0.9)	*80*	96	4	0
Combined lithium + divalproex	5.8(1.6)	*4*	39	54	7
Divalproex monotherapy	5.8(1.7)	*4*	36	54	11
Lithium plus antidepressant	5.1(2.0)	*4*	23	54	23
Divalproex + antidepressant	4.3(1.8)	*0*	5	59	36
Add or substitute another putative mood stabilizer	4.2(2.0)	*0*	14	50	36
Lithium + divalproex + antidepressant	4.2(2.2)	*6*	9	53	38
2b. Acute phase regimen was divalproex alone					
Divalproex monotherapy	8.2(1.5)	*63*	91	5	4
Lithium monotherapy	6.1(1.8)	*9*	39	52	9
Combined lithium + divalproex	6.0(1.8)	*9*	45	50	5
Divalproex + antidepressant	5.1(2.2)	*5*	21	54	25
Lithium plus antidepressant	4.4(1.9)	*0*	11	55	35
Lithium + divalproex + antidepressant	4.3(2.2)	*6*	11	53	36
Add or substitute another putative mood stabilizer	4.2(2.0)	*0*	13	52	36
2c. Acute phase regimen was lithium + divalproex					
Combined lithium + divalproex	8.3(1.4)	*66*	89	11	0
Lithium monotherapy	5.5(2.1)	*9*	35	44	22
Divalproex monotherapy	5.5(2.1)	*9*	35	42	24
Lithium + divalproex + antidepressant	5.2(2.5)	*11*	28	45	26
Add or substitute another putative mood stabilizer	4.4(2.1)	*4*	16	49	35
Divalproex + antidepressant	4.4(1.8)	*2*	9	53	38
Lithium plus antidepressant	4.3(1.8)	*0*	9	52	39
		%	%	%	%

9 Long-term maintenance after a manic episode, *continued*



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
SITUATION 3: Patient had some prior severe depressions; never treated with antidepressants					
3a. Acute phase regimen was lithium alone					
Lithium monotherapy	8.4(1.5)	*73*	91	7	2
Combined lithium + divalproex	6.0(1.6)	*6*	42	53	6
Divalproex monotherapy	5.7(1.6)	*6*	29	60	11
Lithium plus antidepressant	5.1(2.2)	*11*	26	51	24
Lithium + divalproex + antidepressant	4.2(2.1)	*4*	11	50	39
Divalproex + antidepressant	4.1(1.9)	*2*	11	51	38
Add or substitute another putative mood stabilizer	3.9(1.9)	*0*	11	44	46
3b. Acute phase regimen was divalproex alone					
Divalproex monotherapy	8.2(1.4)	*61*	87	11	2
Combined lithium + divalproex	6.2(1.6)	*7*	48	46	6
Lithium monotherapy	5.8(1.9)	*4*	41	44	15
Divalproex + antidepressant	4.9(2.2)	*6*	28	41	32
Lithium + divalproex + antidepressant	4.3(2.2)	*8*	13	49	38
Lithium plus antidepressant	4.3(1.9)	*0*	9	52	39
Add or substitute another	3.9(2.0)	*0*	9	46	44
3c. Acute phase regimen was lithium + divalproex					
Combined lithium + divalproex	8.2(1.4)	*63*	89	9	2
Lithium monotherapy	5.7(2.1)	*7*	39	44	17
Divalproex monotherapy	5.6(2.0)	*9*	33	50	17
Lithium + divalproex + antidepressant	4.9(2.3)	*9*	23	45	32
Lithium plus antidepressant	4.3(1.8)	*2*	9	54	37
Divalproex + antidepressant	4.2(1.9)	*2*	9	52	39
Add or substitute another putative mood stabilizer	4.1(2.0)	*4*	11	52	37
		%	%	%	%

10 **Choice of agents for long-term antipsychotic maintenance.** Suppose you have determined that a patient needs long-term maintenance with an oral antipsychotic along with a mood stabilizer. Regardless of your recommendation for choice of antipsychotics during the acute phase, please rate each of the following for long-term use in this situation.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Olanzapine	7.8(1.3)	*41*	86	13	2
Risperidone	7.1(1.5)	*18*	75	23	2
Quetiapine	6.3(1.5)	*4*	48	46	5
Mid-potency conventional antipsychotic	4.9(1.4)	*0*	14	64	21
High-potency conventional antipsychotic	4.7(1.5)	*0*	11	67	22
Molindone	4.3(1.5)	*0*	7	57	36
Loxapine	4.3(1.4)	*0*	4	63	34
Low-potency conventional antipsychotic	3.9(1.4)	*0*	4	57	39
Combined conventional and atypical antipsychotics	3.6(1.8)	*0*	9	36	55
		%	%	%	%

11 **Adequate dose and duration of mood stabilizers.** Please write in the average dose (total mg per 24 hours) or blood level you recommend for each of the following medications to assure an adequate trial in a medically healthy young adult with bipolar disorder during specific phases of treatment. In the last columns on the right, please indicate the length of an adequate trial, measuring from the time you first began the medication and assuming the quickest possible titration up to at least your target dose.

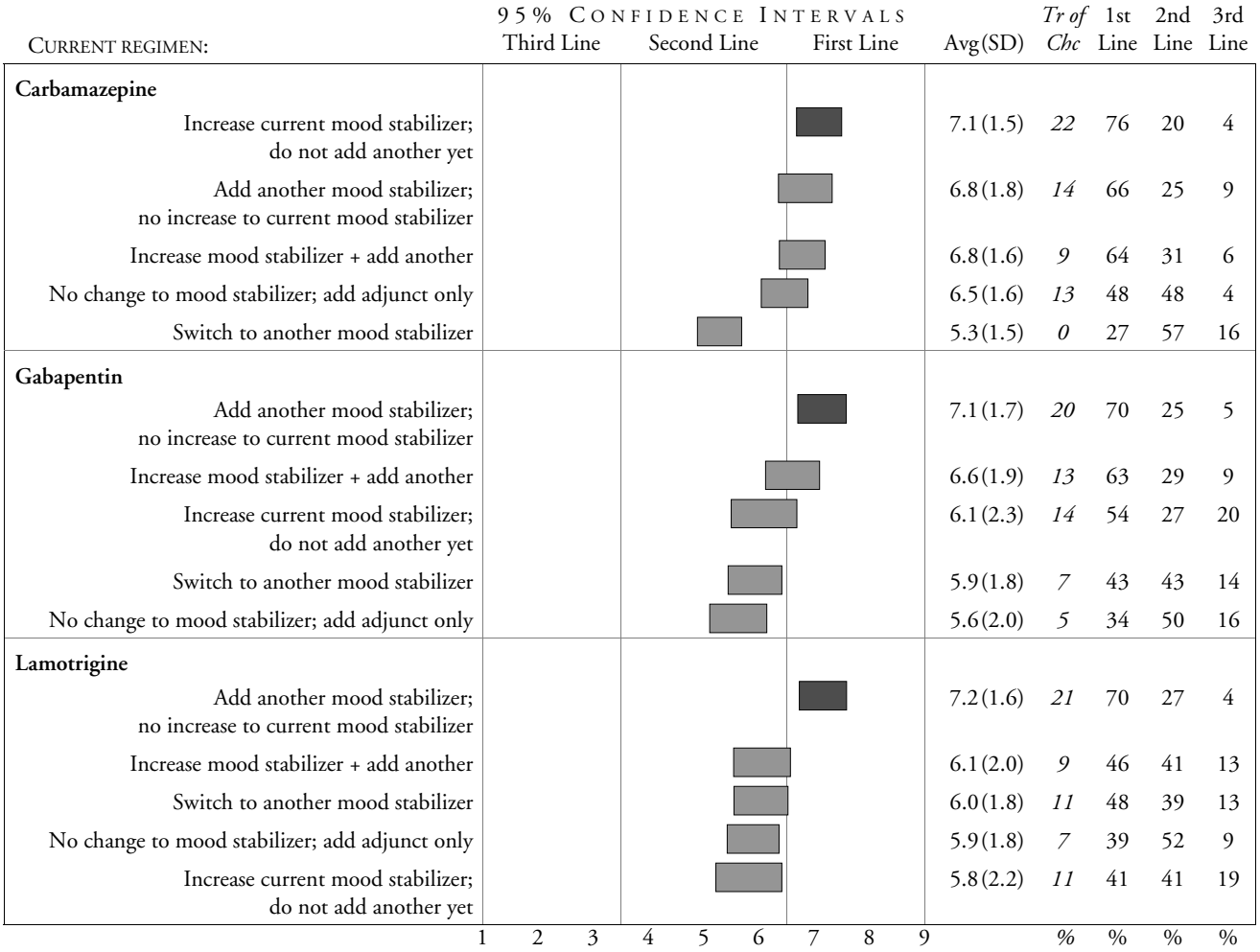
Medication (doses in mg/day unless otherwise noted)	**Treatment of acute mania**				**Long-term maintenance**	
	Starting dose	**Average target dose/level**		**Usual highest final dose/level**	**LOW average dose/level**	**HIGH average dose/level**
		Low	**High**			
	Avg(SD)	Avg(SD)	Avg(SD)	Avg(SD)	Avg(SD)	Avg(SD)
Carbamazepine	406(128)	567(183)	1379(431)			
Carbamazepine level, µg/mL		6.06(2.6)	12.6(4.2)	10.9(1.8)	5.65(1.5)	10.8(2.2)
Divalproex or valproate	863(335)	871(318)	2710(952)			
Loading dose, mg/kg/day	20.5 (2.7)					
Valproic acid level, µg/mL		58.9(14.9)	120(16.6)	109(21.6)	56.6(12)	109(17)
Gabapentin	705(254)	1107(441)	3209(942)	2960(999)	1021(398)	2761(1006)
Lamotrigine	31.9(12.3)	91.2(46.1)	333(128)	282(147)	100(50)	266(125)
Lithium	844(206)	843(265)	2112(617)			
Lithium level, mEq/L		0.73(0.14)	1.21(0.14)	1.16(0.21)	0.63(0.1)	1.07(0.14)
Tiagabine	5.0(2.3)	12.8(10.5)	34.3(18.2)	30.3(16.2)	13.0(8.9)	26.8(11.1)
Topiramate	50(41)	114(58)	427(249)	355(252)	126(78)	340(181)

Duration	**Partial response**		**No response**	
	Fewest days Avg(SD)	**Most days** Avg(SD)	**Fewest days** Avg(SD)	**Most days** Avg(SD)
Carbamazepine	13.0(8.8)	25.4(14.1)	8.8(4.9)	16.9(7.4)
Valproic acid	12.8(9.0)	24.3(14.1)	8.0(4.9)	15.6(7.4)
Gabapentin	12.8(5.9)	24.5(13.2)	8.8(4.7)	16.0(7.2)
Lamotrigine	17.7(10.8)	30.6(16.6)	13.6(9.9)	24.4(18.8)
Lithium	14.5(9.2)	25.8(14.6)	10.0(5.4)	17.7(7.8)
Tiagabine	15.7(8.0)	25.8(12.2)	11.3(7.1)	19.2(10.4)
Topiramate	17.6(15.0)	28.5(17.2)	10.9(6.3)	18.8(10.2)

12 **Breakthrough mania during maintenance on lithium and/or divalproex.** Consider a patient who has had 2 manic episodes (nonpsychotic) and has never taken antidepressants. Each episode responded to the same regimen of high-dose mood stabilizer(s) + antipsychotic. The antipsychotic was tapered rapidly after remission, while the mood stabilizer was continued at either a high or low dose. Six months after resolution of the second episode, the patient is continuing to take the same mood stabilizer(s) that was effective in the acute phases. Unfortunately, the patient now shows rapidly escalating signs of impending mania and you must intervene to avert a full-blown episode. Please rate the following options in each of 3 situations, depending in each situation on the current maintenance regimen.

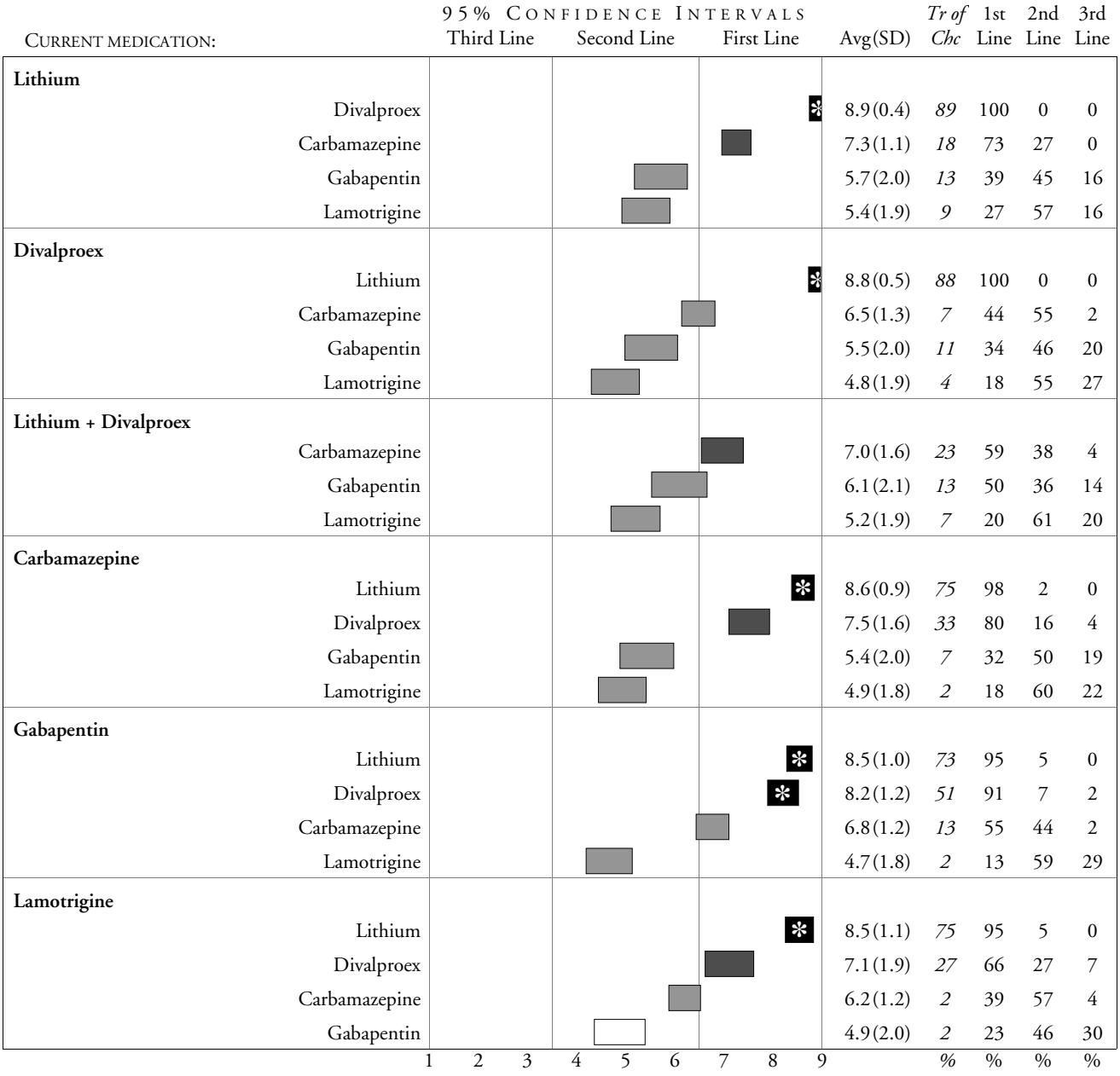
CURRENT REGIMEN:	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lithium Alone, LOW Dose						
Increase current mood stabilizer; do not add another yet		8.4(0.9)	*61*	95	5	0
Increase mood stabilizer + add another		6.7(1.7)	*13*	64	31	6
Add another mood stabilizer		6.0(1.7)	*6*	42	47	11
No change to mood stabilizer; add adjuncts only		5.0(1.9)	*2*	16	57	27
Switch to another mood stabilizer		4.0(1.7)	*2*	5	52	43
Lithium Alone, HIGH Dose						
Add another mood stabilizer		8.1(1.1)	*46*	88	13	0
No change to mood stabilizer; add adjuncts only		7.3(1.7)	*29*	73	23	4
Switch to another mood stabilizer		5.5(1.8)	*4*	25	57	18
Divalproex Alone, LOW Dose						
Increase current mood stabilizer; do not add another yet		8.3(1.0)	*57*	95	5	0
Increase mood stabilizer + add another		6.6(1.7)	*11*	64	30	6
Add another mood stabilizer		6.1(1.7)	*7*	38	51	11
No change to mood stabilizer; add adjuncts only		4.9(1.9)	*2*	18	55	27
Switch to another mood stabilizer		4.0(1.7)	*0*	7	47	46
Divalproex Alone, HIGH Dose						
Add another mood stabilizer		8.2(1.1)	*54*	91	9	0
No change to mood stabilizer; add adjuncts only		7.1(1.8)	*26*	62	35	4
Switch to another mood stabilizer		5.3(1.8)	*4*	23	57	20
Lithium+Divalproex at MAXIMUM Tolerable Doses						
No change to mood stabilizer; add adjuncts only		7.8(1.8)	*52*	80	16	4
Add another mood stabilizer		7.4(1.5)	*30*	75	21	4
Switch to another mood stabilizer		5.9(1.8)	*7*	43	46	11
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

13 **Breakthrough mania during maintenance on alternative anticonvulsants.** Consider the same case history as in the previous question, except that the patient has been maintained on carbamazepine, gabapentin, or lamotrigine at the same dose that worked during the acute phase, is tolerating this dose without major side effects, and has never taken other mood stabilizers.



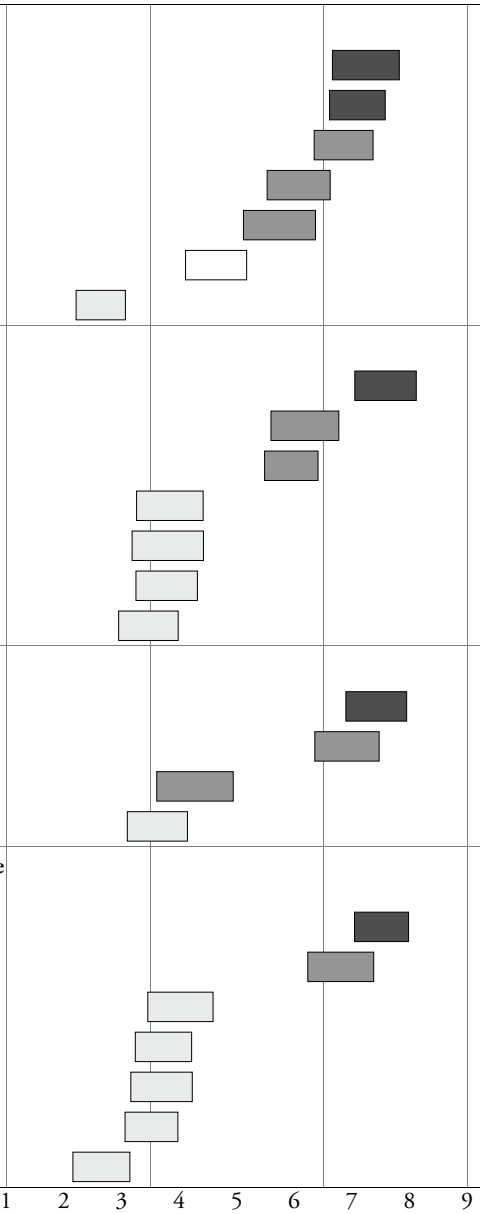
CURRENT REGIMEN:	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Carbamazepine					
Increase current mood stabilizer; do not add another yet	7.1 (1.5)	*22*	76	20	4
Add another mood stabilizer; no increase to current mood stabilizer	6.8 (1.8)	*14*	66	25	9
Increase mood stabilizer + add another	6.8 (1.6)	*9*	64	31	6
No change to mood stabilizer; add adjunct only	6.5 (1.6)	*13*	48	48	4
Switch to another mood stabilizer	5.3 (1.5)	*0*	27	57	16
Gabapentin					
Add another mood stabilizer; no increase to current mood stabilizer	7.1 (1.7)	*20*	70	25	5
Increase mood stabilizer + add another	6.6 (1.9)	*13*	63	29	9
Increase current mood stabilizer; do not add another yet	6.1 (2.3)	*14*	54	27	20
Switch to another mood stabilizer	5.9 (1.8)	*7*	43	43	14
No change to mood stabilizer; add adjunct only	5.6 (2.0)	*5*	34	50	16
Lamotrigine					
Add another mood stabilizer; no increase to current mood stabilizer	7.2 (1.6)	*21*	70	27	4
Increase mood stabilizer + add another	6.1 (2.0)	*9*	46	41	13
Switch to another mood stabilizer	6.0 (1.8)	*11*	48	39	13
No change to mood stabilizer; add adjunct only	5.9 (1.8)	*7*	39	52	9
Increase current mood stabilizer; do not add another yet	5.8 (2.2)	*11*	41	41	19
		%	%	%	%

14 **Mood stabilizer choice for add-on treatment of breakthrough mania.** In the above scenarios of breakthrough mania, assume you have decided to incorporate another mood stabilizer. Please rate each of the following options as an add-on mood stabilizer, depending on the current medication.



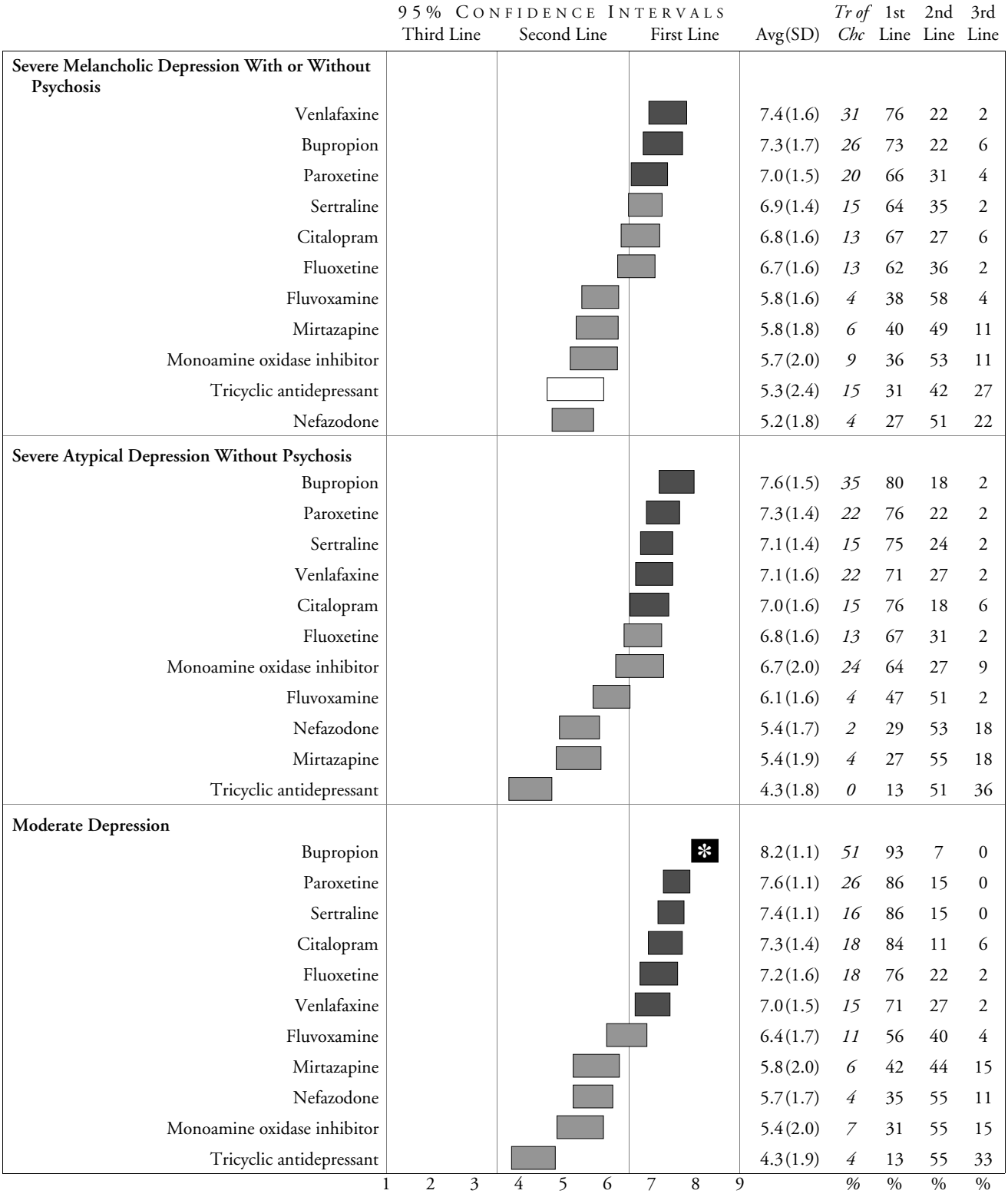
CURRENT MEDICATION:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lithium					
Divalproex	8.9(0.4)	*89*	100	0	0
Carbamazepine	7.3(1.1)	*18*	73	27	0
Gabapentin	5.7(2.0)	*13*	39	45	16
Lamotrigine	5.4(1.9)	*9*	27	57	16
Divalproex					
Lithium	8.8(0.5)	*88*	100	0	0
Carbamazepine	6.5(1.3)	*7*	44	55	2
Gabapentin	5.5(2.0)	*11*	34	46	20
Lamotrigine	4.8(1.9)	*4*	18	55	27
Lithium + Divalproex					
Carbamazepine	7.0(1.6)	*23*	59	38	4
Gabapentin	6.1(2.1)	*13*	50	36	14
Lamotrigine	5.2(1.9)	*7*	20	61	20
Carbamazepine					
Lithium	8.6(0.9)	*75*	98	2	0
Divalproex	7.5(1.6)	*33*	80	16	4
Gabapentin	5.4(2.0)	*7*	32	50	19
Lamotrigine	4.9(1.8)	*2*	18	60	22
Gabapentin					
Lithium	8.5(1.0)	*73*	95	5	0
Divalproex	8.2(1.2)	*51*	91	7	2
Carbamazepine	6.8(1.2)	*13*	55	44	2
Lamotrigine	4.7(1.8)	*2*	13	59	29
Lamotrigine					
Lithium	8.5(1.1)	*75*	95	5	0
Divalproex	7.1(1.9)	*27*	66	27	7
Carbamazepine	6.2(1.2)	*2*	39	57	4
Gabapentin	4.9(2.0)	*2*	23	46	30
		%	%	%	%

15 **Treatment of bipolar major depression: first episode, initial strategy.** A physically healthy young man presents with major depression several years after a single manic episode that was successfully treated. He was tapered off a mood stabilizer and was stable for 1 year off medication. He is currently on no medications. What would be your initial strategy for medication? Please rate each of the following based on the clinical features listed below. Later questions will allow you to rate specific medications. Assume you can use a benzodiazepine for insomnia or agitation with any option.



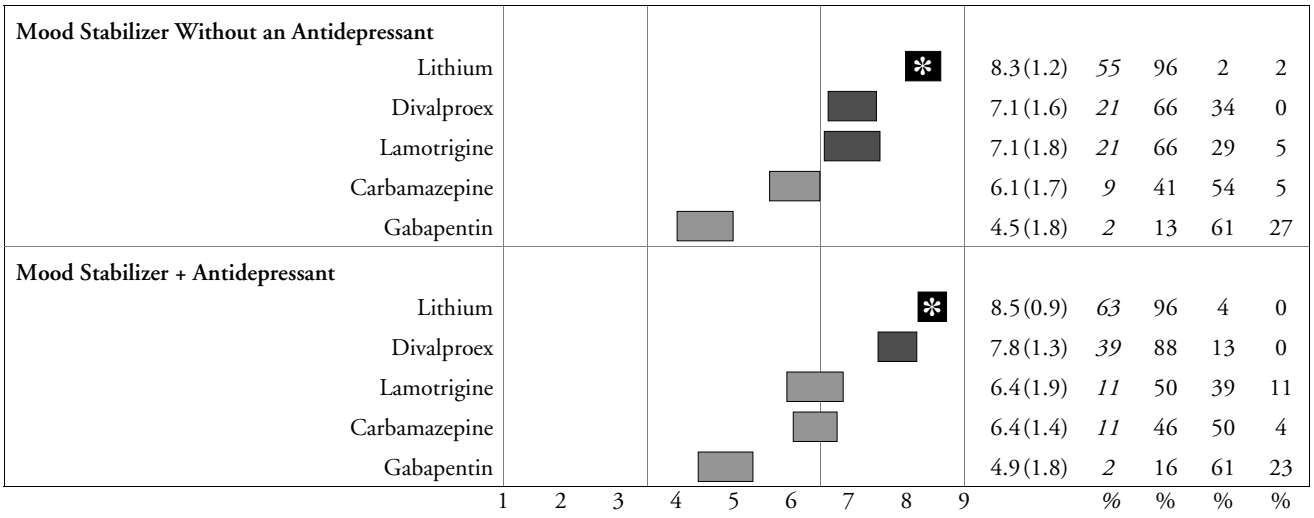
	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Severe Depression With Psychosis					
Antidepressant + mood stabilizer + antipsychotic	7.2 (2.2)	*35*	75	16	9
Electroconvulsive therapy	7.1 (1.8)	*29*	67	29	4
Mood stabilizer + antipsychotic	6.9 (1.9)	*24*	64	31	6
Antidepressant + mood stabilizer	6.1 (2.1)	*13*	49	44	7
Antidepressant + antipsychotic	5.7 (2.3)	*13*	37	43	20
Mood stabilizer	4.6 (2.0)	*4*	22	42	36
Antidepressant	2.6 (1.6)	*0*	2	24	75
Severe Depression Without Psychosis					
Antidepressant + mood stabilizer	7.6 (2.0)	*47*	80	15	6
Mood stabilizer	6.2 (2.2)	*24*	47	40	13
Electroconvulsive therapy	6.0 (1.7)	*7*	42	51	7
Antidepressant + mood stabilizer + antipsychotic	3.8 (2.2)	*0*	15	31	55
Antidepressant	3.8 (2.3)	*2*	15	36	49
Mood stabilizer + antipsychotic	3.8 (2.0)	*0*	6	44	51
Antidepressant + antipsychotic	3.5 (1.9)	*0*	6	41	54
Moderate Depression					
Mood stabilizer	7.4 (2.0)	*47*	73	26	2
Antidepressant + mood stabilizer	6.9 (2.1)	*26*	75	15	11
Antidepressant	4.3 (2.5)	*7*	20	33	47
Electroconvulsive therapy	3.6 (2.0)	*0*	9	36	55
Initial Mania Precipitated by Antidepressant Alone for Supposed Unipolar Depression					
Mood stabilizer	7.5 (1.8)	*40*	76	20	4
Antidepressant + mood stabilizer	6.8 (2.2)	*29*	66	20	15
Electroconvulsive therapy	4.0 (2.1)	*4*	15	35	51
Antidepressant + antipsychotic	3.7 (1.8)	*0*	6	48	46
Antidepressant + mood stabilizer + antipsychotic	3.7 (2.0)	*0*	9	36	55
Mood stabilizer + antipsychotic	3.5 (1.7)	*0*	2	41	57
Antidepressant	2.7 (1.8)	*2*	2	28	70
		%	%	%	%

16 **Treatment of bipolar major depression: first episode, choice of antidepressant.** In the situation described in question 15, assume you have decided to use a standard antidepressant as part of your initial treatment. Please rate each of the following as an initial choice in each of the symptom presentations listed below.



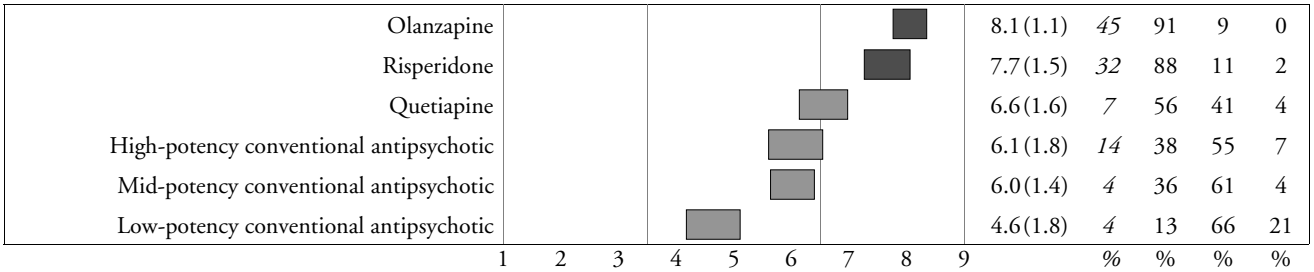
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Severe Melancholic Depression With or Without Psychosis					
Venlafaxine	7.4(1.6)	*31*	76	22	2
Bupropion	7.3(1.7)	*26*	73	22	6
Paroxetine	7.0(1.5)	*20*	66	31	4
Sertraline	6.9(1.4)	*15*	64	35	2
Citalopram	6.8(1.6)	*13*	67	27	6
Fluoxetine	6.7(1.6)	*13*	62	36	2
Fluvoxamine	5.8(1.6)	*4*	38	58	4
Mirtazapine	5.8(1.8)	*6*	40	49	11
Monoamine oxidase inhibitor	5.7(2.0)	*9*	36	53	11
Tricyclic antidepressant	5.3(2.4)	*15*	31	42	27
Nefazodone	5.2(1.8)	*4*	27	51	22
Severe Atypical Depression Without Psychosis					
Bupropion	7.6(1.5)	*35*	80	18	2
Paroxetine	7.3(1.4)	*22*	76	22	2
Sertraline	7.1(1.4)	*15*	75	24	2
Venlafaxine	7.1(1.6)	*22*	71	27	2
Citalopram	7.0(1.6)	*15*	76	18	6
Fluoxetine	6.8(1.6)	*13*	67	31	2
Monoamine oxidase inhibitor	6.7(2.0)	*24*	64	27	9
Fluvoxamine	6.1(1.6)	*4*	47	51	2
Nefazodone	5.4(1.7)	*2*	29	53	18
Mirtazapine	5.4(1.9)	*4*	27	55	18
Tricyclic antidepressant	4.3(1.8)	*0*	13	51	36
Moderate Depression					
Bupropion	8.2(1.1)	*51*	93	7	0
Paroxetine	7.6(1.1)	*26*	86	15	0
Sertraline	7.4(1.1)	*16*	86	15	0
Citalopram	7.3(1.4)	*18*	84	11	6
Fluoxetine	7.2(1.6)	*18*	76	22	2
Venlafaxine	7.0(1.5)	*15*	71	27	2
Fluvoxamine	6.4(1.7)	*11*	56	40	4
Mirtazapine	5.8(2.0)	*6*	42	44	15
Nefazodone	5.7(1.7)	*4*	35	55	11
Monoamine oxidase inhibitor	5.4(2.0)	*7*	31	55	15
Tricyclic antidepressant	4.3(1.9)	*4*	13	55	33
		%	%	%	%

17 **Treatment of bipolar major depression: first episode, choice of mood stabilizer for acute phase.** In the situation of the previous question, assume you have decided to use a mood stabilizer as part of your initial plan for a currently unmedicated patient. Please rate each of the following choices of mood stabilizer, depending on whether or not you have also decided to use an antidepressant. Assume that none of the mood stabilizers had previously failed in the acute-phase or preventive treatment of this patient's mania.



	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mood Stabilizer Without an Antidepressant					
Lithium	8.3 (1.2)	*55*	96	2	2
Divalproex	7.1 (1.6)	*21*	66	34	0
Lamotrigine	7.1 (1.8)	*21*	66	29	5
Carbamazepine	6.1 (1.7)	*9*	41	54	5
Gabapentin	4.5 (1.8)	*2*	13	61	27
Mood Stabilizer + Antidepressant					
Lithium	8.5 (0.9)	*63*	96	4	0
Divalproex	7.8 (1.3)	*39*	88	13	0
Lamotrigine	6.4 (1.9)	*11*	50	39	11
Carbamazepine	6.4 (1.4)	*11*	46	50	4
Gabapentin	4.9 (1.8)	*2*	16	61	23
		%	%	%	%

18 **Bipolar depression with psychosis: choice of antipsychotic.** Assume you have decided to use an antipsychotic in the acute-phase treatment of a patient with bipolar depression with psychotic features. Please rate the following options.

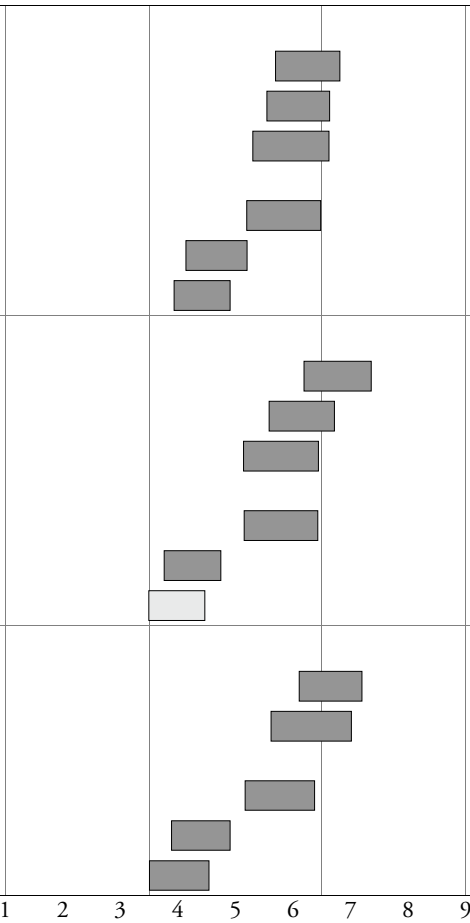


	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Olanzapine	8.1 (1.1)	*45*	91	9	0
Risperidone	7.7 (1.5)	*32*	88	11	2
Quetiapine	6.6 (1.6)	*7*	56	41	4
High-potency conventional antipsychotic	6.1 (1.8)	*14*	38	55	7
Mid-potency conventional antipsychotic	6.0 (1.4)	*4*	36	61	4
Low-potency conventional antipsychotic	4.6 (1.8)	*4*	13	66	21
		%	%	%	%

19 **Bipolar depression, successful acute-phase treatment of first episode: how long to continue medication.** Consider a patient who has had 2 manic episodes, the last one ending 6 months ago. During maintenance treatment with a mood stabilizer, the patient recently developed a major depression, which has remitted with the addition of an antidepressant (plus an antipsychotic for psychotic depression). Assuming you plan to continue the mood stabilizer indefinitely, how long would you continue the antidepressant or antipsychotic before beginning to gradually taper (from 25% per week to 25% per month), depending on the severity of the depression?

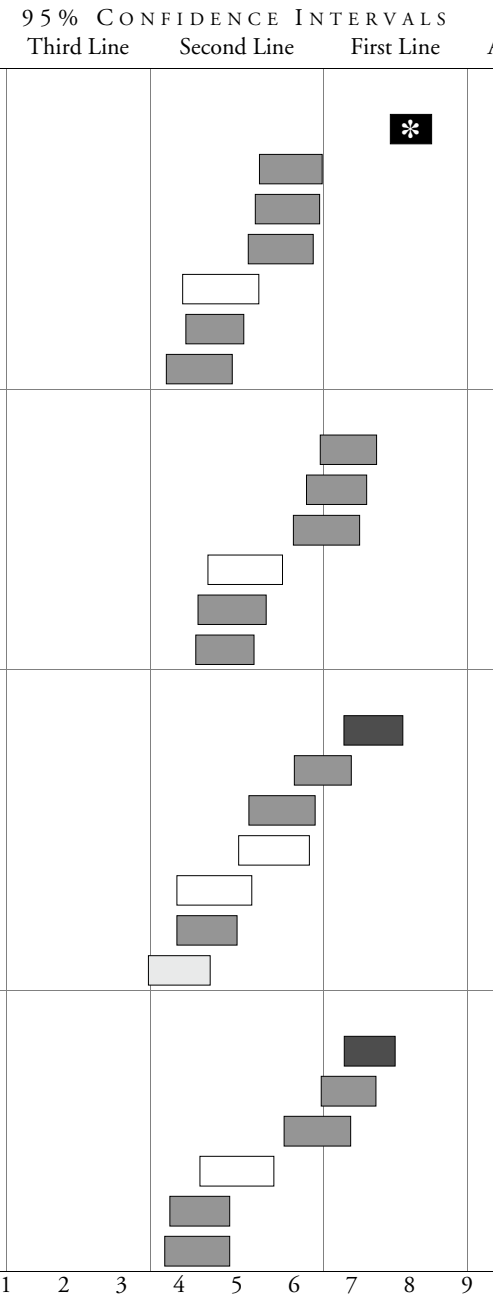
	Minimum weeks	Maximum weeks	Indefinitely
	Avg (SD)	Avg (SD)	%
Antidepressant after severe depression with psychotic features	9.1 (5.6)	23.6 (13.1)	23.2
Antidepressant after severe depression without psychotic features	9.2 (5.5)	22.5 (11.8)	23.2
Antidepressant after moderate depression	8.0 (5.3)	20.2 (10.2)	16.1
Antipsychotic after psychotic depression	7.1 (4.6)	22.3 (12.4)	7.1

20 **First episode of bipolar depression: breakthrough on mood stabilizer immediately after a manic episode.** Suppose a patient has just recovered from a first or second manic episode after treatment with lithium, divalproex, or a combination of both. The patient is taking maximum tolerable doses of these medications and modest doses of adjuncts. Within days of recovering, the patient develops symptoms of depression, progressing steadily over 2 weeks to moderate severity. The patient is not psychotic or suicidal, is euthyroid, has never taken antidepressants, and is receiving appropriate psychotherapy. Depending on the current mood stabilizer regimen, please rate the possible next steps.



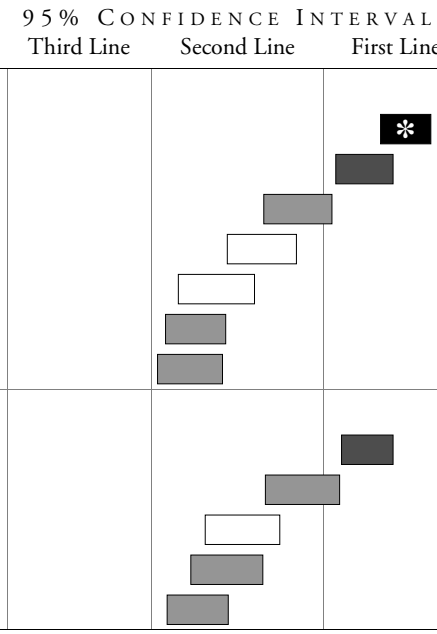
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Currently Taking Lithium Alone					
Add lamotrigine	6.3(2.0)	*10*	48	42	10
Add an antidepressant	6.1(1.9)	*6*	44	50	6
No new medication yet; supportive, watchful waiting for a few weeks unless patient deteriorates	6.0(2.3)	*11*	49	34	17
Add divalproex	5.8(2.3)	*10*	48	33	19
Add carbamazepine	4.7(1.9)	*0*	15	52	33
Add thyroid hormone	4.4(1.7)	*0*	10	63	27
Currently Taking Divalproex Alone					
Add lithium	6.8(2.1)	*25*	65	25	10
Add an antidepressant	6.2(2.0)	*8*	44	50	6
No new medication yet; supportive, watchful waiting for a few weeks unless patient deteriorates	5.8(2.2)	*11*	40	45	15
Add lamotrigine	5.8(2.3)	*11*	43	40	17
Add carbamazepine	4.3(1.7)	*0*	8	54	38
Add thyroid hormone	4.0(1.7)	*0*	6	55	38
Currently Taking Lithium + Divalproex					
Add an antidepressant	6.7(1.9)	*19*	56	38	6
No new medication yet; supportive, watchful waiting for a few weeks unless patient deteriorates	6.3(2.5)	*25*	58	27	15
Add lamotrigine	5.8(2.1)	*6*	38	45	17
Add thyroid hormone	4.4(1.8)	*0*	10	58	31
Add carbamazepine	4.0(1.8)	*0*	6	54	40
		%	%	%	%

21 **First episode of bipolar depression: breakthrough on mood stabilizer delayed some time after a manic episode.** Consider again a patient who has recovered from a first or second manic episode and has never taken antidepressants. Now, after a significant period of remission (e.g., 15 months) on mood stabilizer(s) alone, the patient develops signs of moderately severe depression for 2 weeks, without psychosis or suicidality. The patient is euthyroid and receiving appropriate psychotherapy. Please rate the following options. Note that we ask about 2 regimens: 1) the patient taking relatively low doses of mood stabilizer and 2) the patient already on maximum tolerable doses.



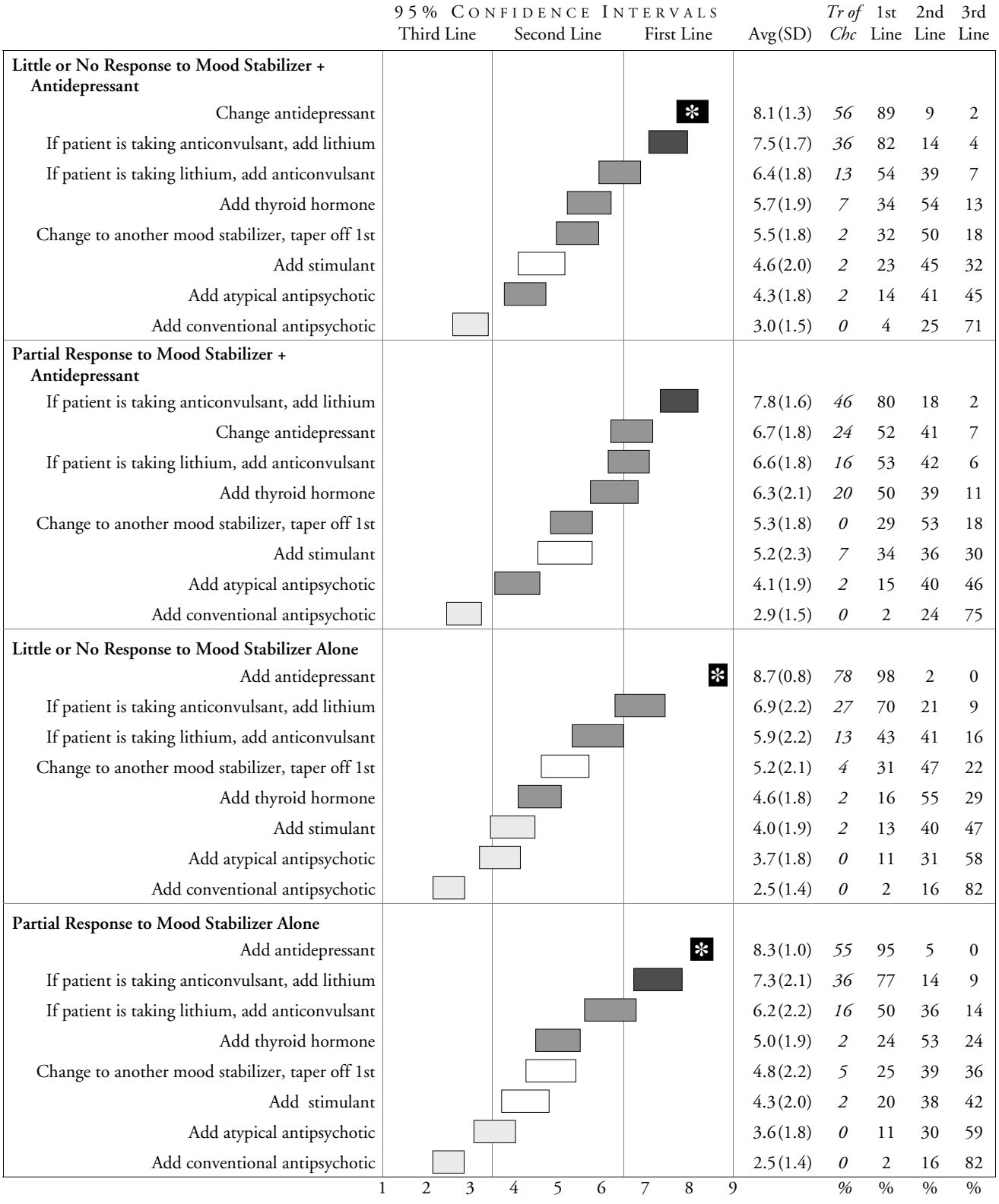
CURRENT REGIMEN:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lithium Alone, LOW Dose					
Increase lithium	8.0(1.3)	*56*	88	13	0
Add divalproex	5.9(1.9)	*9*	40	49	11
Add lamotrigine	5.9(2.0)	*4*	42	46	13
Add antidepressant	5.8(1.9)	*0*	48	39	13
Watchful waiting	4.7(2.3)	*4*	24	43	33
Add carbamazepine	4.6(1.8)	*0*	15	55	30
Add thyroid hormone	4.4(2.0)	*2*	11	57	33
Lithium Alone, HIGH Dose					
Add antidepressant	6.9(1.7)	*17*	65	31	4
Add lamotrigine	6.7(1.8)	*13*	60	33	6
Add divalproex	6.6(2.0)	*19*	60	32	9
Watchful waiting	5.2(2.3)	*6*	33	44	23
Add thyroid hormone	4.9(2.1)	*2*	21	56	23
Add carbamazepine	4.8(1.8)	*0*	17	60	23
Divalproex Alone, LOW Dose					
Increase divalproex	7.4(1.8)	*33*	78	17	4
Add lithium	6.5(1.7)	*11*	53	43	4
Add antidepressant	5.8(2.0)	*0*	48	37	15
Add lamotrigine	5.7(2.2)	*4*	40	40	21
Watchful waiting	4.6(2.3)	*4*	22	46	33
Add carbamazepine	4.5(1.8)	*0*	15	56	29
Add thyroid hormone	4.0(1.9)	*0*	9	53	38
Divalproex Alone, HIGH Dose					
Add lithium	7.3(1.5)	*26*	72	26	2
Add antidepressant	6.9(1.7)	*17*	63	33	4
Add lamotrigine	6.4(2.0)	*10*	54	35	10
Watchful waiting	5.0(2.3)	*6*	29	46	25
Add carbamazepine	4.4(1.8)	*0*	15	54	31
Add thyroid hormone	4.3(2.0)	*0*	13	52	35
		%	%	%	%

21 First episode of bipolar depression: breakthrough on mood stabilizer delayed some time after a manic episode, *continued*



CURRENT REGIMEN:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lithium + Divalproex, Both LOW Dose					
Increase lithium	7.9(1.5)	*53*	89	9	2
Increase divalproex	7.2(1.7)	*22*	80	16	4
Add antidepressant	6.0(2.0)	*9*	52	33	15
Add lamotrigine	5.4(2.1)	*2*	38	40	23
Watchful waiting	4.6(2.3)	*4*	26	39	35
Add carbamazepine	4.3(1.8)	*0*	15	52	33
Add thyroid hormone	4.2(2.0)	*0*	11	55	34
Lithium + Divalproex, Both HIGH Dose					
Add antidepressant	7.3(1.6)	*23*	71	25	4
Add lamotrigine	6.1(2.3)	*13*	54	29	17
Watchful waiting	5.1(2.3)	*6*	33	42	25
Add thyroid hormone	4.8(2.2)	*4*	23	50	27
Add carbamazepine	4.3(1.8)	*0*	13	54	33
		%	%	%	%

22 **Bipolar depression, acute phase: next step strategy for inadequate response.** In the case of moderate to severe depression without psychosis, please rate each of the following options as your next step if the depression persists after an adequate trial with your first treatment strategy, depending on degree of response and initial strategy. Please note that you will be able to choose specific antidepressants and anticonvulsants in subsequent questions.



	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Little or No Response to Mood Stabilizer + Antidepressant					
Change antidepressant	8.1 (1.3)	*56*	89	9	2
If patient is taking anticonvulsant, add lithium	7.5 (1.7)	*36*	82	14	4
If patient is taking lithium, add anticonvulsant	6.4 (1.8)	*13*	54	39	7
Add thyroid hormone	5.7 (1.9)	*7*	34	54	13
Change to another mood stabilizer, taper off 1st	5.5 (1.8)	*2*	32	50	18
Add stimulant	4.6 (2.0)	*2*	23	45	32
Add atypical antipsychotic	4.3 (1.8)	*2*	14	41	45
Add conventional antipsychotic	3.0 (1.5)	*0*	4	25	71
Partial Response to Mood Stabilizer + Antidepressant					
If patient is taking anticonvulsant, add lithium	7.8 (1.6)	*46*	80	18	2
Change antidepressant	6.7 (1.8)	*24*	52	41	7
If patient is taking lithium, add anticonvulsant	6.6 (1.8)	*16*	53	42	6
Add thyroid hormone	6.3 (2.1)	*20*	50	39	11
Change to another mood stabilizer, taper off 1st	5.3 (1.8)	*0*	29	53	18
Add stimulant	5.2 (2.3)	*7*	34	36	30
Add atypical antipsychotic	4.1 (1.9)	*2*	15	40	46
Add conventional antipsychotic	2.9 (1.5)	*0*	2	24	75
Little or No Response to Mood Stabilizer Alone					
Add antidepressant	8.7 (0.8)	*78*	98	2	0
If patient is taking anticonvulsant, add lithium	6.9 (2.2)	*27*	70	21	9
If patient is taking lithium, add anticonvulsant	5.9 (2.2)	*13*	43	41	16
Change to another mood stabilizer, taper off 1st	5.2 (2.1)	*4*	31	47	22
Add thyroid hormone	4.6 (1.8)	*2*	16	55	29
Add stimulant	4.0 (1.9)	*2*	13	40	47
Add atypical antipsychotic	3.7 (1.8)	*0*	11	31	58
Add conventional antipsychotic	2.5 (1.4)	*0*	2	16	82
Partial Response to Mood Stabilizer Alone					
Add antidepressant	8.3 (1.0)	*55*	95	5	0
If patient is taking anticonvulsant, add lithium	7.3 (2.1)	*36*	77	14	9
If patient is taking lithium, add anticonvulsant	6.2 (2.2)	*16*	50	36	14
Add thyroid hormone	5.0 (1.9)	*2*	24	53	24
Change to another mood stabilizer, taper off 1st	4.8 (2.2)	*5*	25	39	36
Add stimulant	4.3 (2.0)	*2*	20	38	42
Add atypical antipsychotic	3.6 (1.8)	*0*	11	30	59
Add conventional antipsychotic	2.5 (1.4)	*0*	2	16	82
		%	%	%	%

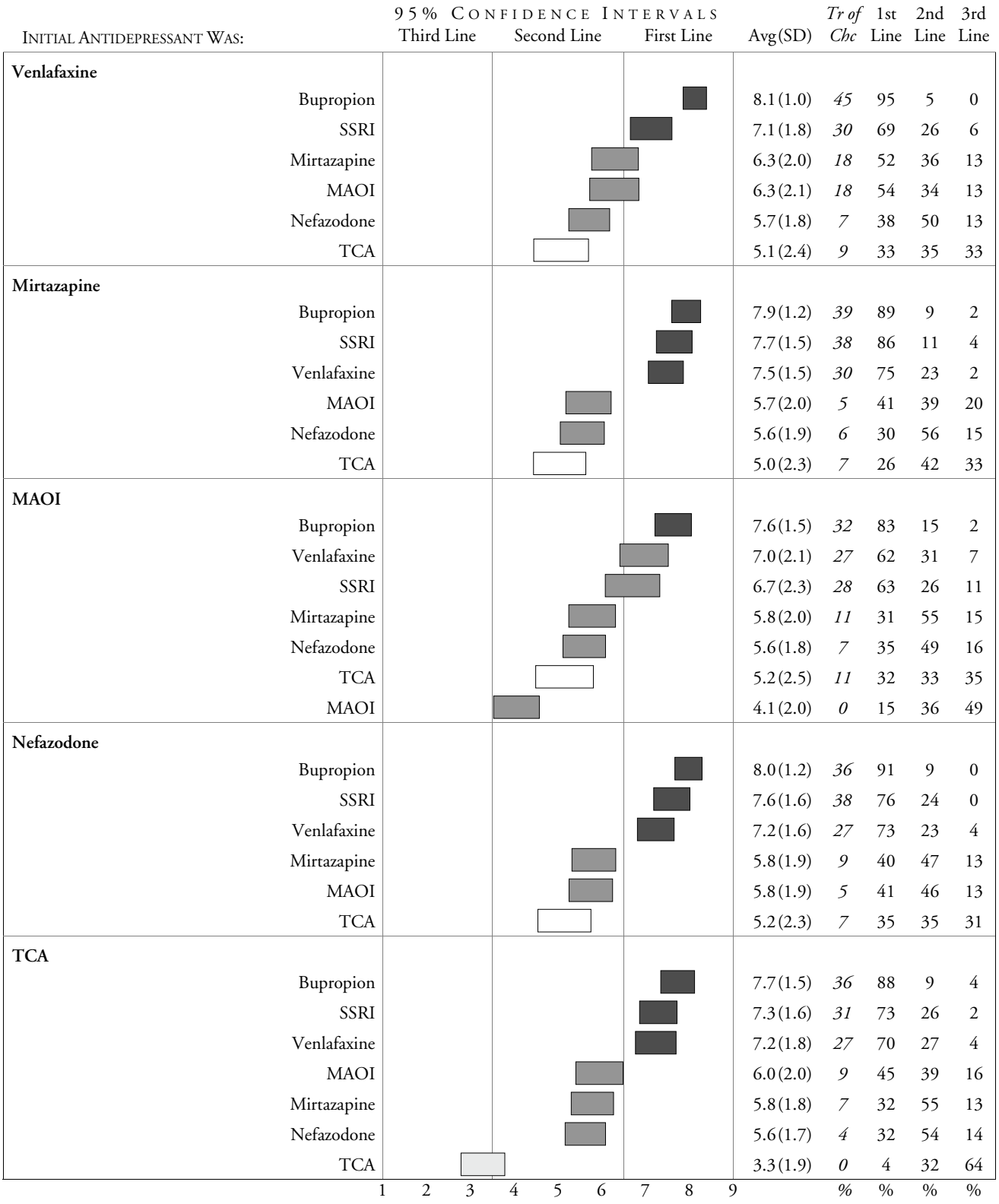
23 **Bipolar depression with psychotic features: next step strategy for inadequate response.** Now we turn to inadequate response in severe psychotic depression. If there has been little or no response to your initial strategy, please rate each of the following next steps. Please note that we ask about specific medication options in later questions.

INITIAL STRATEGY	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Mood Stabilizer + Antipsychotic						
Add an antidepressant		8.6(0.7)	*70*	98	2	0
If patient is taking anticonvulsant, add lithium		7.5(1.8)	*38*	77	18	5
If patient is taking lithium, add anticonvulsant		6.7(2.0)	*21*	54	39	7
Change antipsychotic		6.2(1.5)	*7*	43	52	5
Add thyroid hormone		4.5(1.8)	*0*	14	55	30
Add stimulant		3.3(1.7)	*0*	4	38	58
Antidepressant + Mood Stabilizer + Antipsychotic						
Change the antidepressant		8.1(0.9)	*45*	95	5	0
If patient is taking anticonvulsant, add lithium		7.6(1.7)	*41*	82	11	7
If patient is taking lithium, add anticonvulsant		6.8(2.0)	*25*	59	30	11
Change antipsychotic		6.5(1.5)	*7*	59	38	4
Add thyroid hormone		5.1(2.0)	*4*	27	52	21
Add stimulant		3.5(1.7)	*0*	4	46	50
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

24 **Bipolar depression, inadequate response: choice of next antidepressant.** Suppose that a patient with moderate to severe depression has received an antidepressant plus a mood stabilizer (plus an antipsychotic if psychosis is present), but that despite an adequate dose and duration of antidepressant has achieved little or no response. Suppose you then decide to add or switch to a second antidepressant. Please rate the appropriateness of the following options, depending on the antidepressant used in the initial treatment. When the same class appears in the column and row, we are asking you to rate a switch to another member of the same class (e.g., from SSRI to SSRI).

INITIAL ANTIDEPRESSANT WAS:	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Bupropion						
Selective serotonin reuptake inhibitor (SSRI)		8.1(1.3)	*55*	87	13	0
Venlafaxine		7.7(1.4)	*38*	75	25	0
Monoamine oxidase inhibitor (MAOI)		6.1(2.0)	*13*	50	36	14
Mirtazapine		6.1(1.9)	*16*	39	50	11
Nefazodone		5.8(1.7)	*9*	34	55	11
Tricyclic antidepressant (TCA)		5.3(2.2)	*11*	29	40	31
SSRI						
Bupropion		8.3(1.0)	*54*	95	5	0
Venlafaxine		7.6(1.4)	*36*	77	21	2
Mirtazapine		6.3(2.0)	*16*	50	39	11
MAOI		6.0(1.9)	*7*	48	39	13
Nefazodone		5.9(1.7)	*9*	34	59	7
TCA		5.5(2.4)	*15*	36	36	27
SSRI		5.4(1.9)	*4*	32	52	16
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

24 Bipolar depression, inadequate response: choice of next antidepressant, *continued*

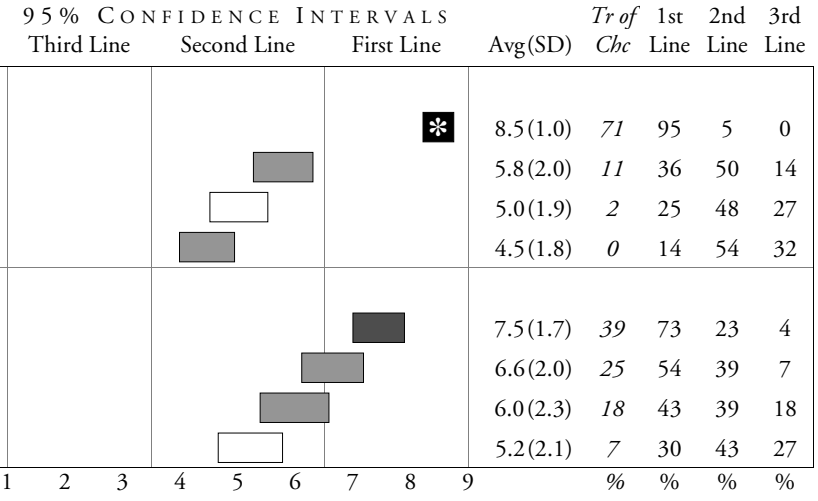


Initial Antidepressant Was:	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Venlafaxine					
Bupropion	8.1 (1.0)	*45*	95	5	0
SSRI	7.1 (1.8)	*30*	69	26	6
Mirtazapine	6.3 (2.0)	*18*	52	36	13
MAOI	6.3 (2.1)	*18*	54	34	13
Nefazodone	5.7 (1.8)	*7*	38	50	13
TCA	5.1 (2.4)	*9*	33	35	33
Mirtazapine					
Bupropion	7.9 (1.2)	*39*	89	9	2
SSRI	7.7 (1.5)	*38*	86	11	4
Venlafaxine	7.5 (1.5)	*30*	75	23	2
MAOI	5.7 (2.0)	*5*	41	39	20
Nefazodone	5.6 (1.9)	*6*	30	56	15
TCA	5.0 (2.3)	*7*	26	42	33
MAOI					
Bupropion	7.6 (1.5)	*32*	83	15	2
Venlafaxine	7.0 (2.1)	*27*	62	31	7
SSRI	6.7 (2.3)	*28*	63	26	11
Mirtazapine	5.8 (2.0)	*11*	31	55	15
Nefazodone	5.6 (1.8)	*7*	35	49	16
TCA	5.2 (2.5)	*11*	32	33	35
MAOI	4.1 (2.0)	*0*	15	36	49
Nefazodone					
Bupropion	8.0 (1.2)	*36*	91	9	0
SSRI	7.6 (1.6)	*38*	76	24	0
Venlafaxine	7.2 (1.6)	*27*	73	23	4
Mirtazapine	5.8 (1.9)	*9*	40	47	13
MAOI	5.8 (1.9)	*5*	41	46	13
TCA	5.2 (2.3)	*7*	35	35	31
TCA					
Bupropion	7.7 (1.5)	*36*	88	9	4
SSRI	7.3 (1.6)	*31*	73	26	2
Venlafaxine	7.2 (1.8)	*27*	70	27	4
MAOI	6.0 (2.0)	*9*	45	39	16
Mirtazapine	5.8 (1.8)	*7*	32	55	13
Nefazodone	5.6 (1.7)	*4*	32	54	14
TCA	3.3 (1.9)	*0*	4	32	64
		%	%	%	%

25 **Bipolar depression, inadequate response: choice of next mood stabilizer.** In the situation described in question 24 of inadequate response of moderate to severe depression to antidepressant plus a mood stabilizer (plus antipsychotic if needed), suppose you decide to leave the antidepressant unchanged and instead decide to add or switch to a second mood stabilizer. Please rate the appropriateness of the following options for the second mood stabilizer you would use, depending on the initial choice.

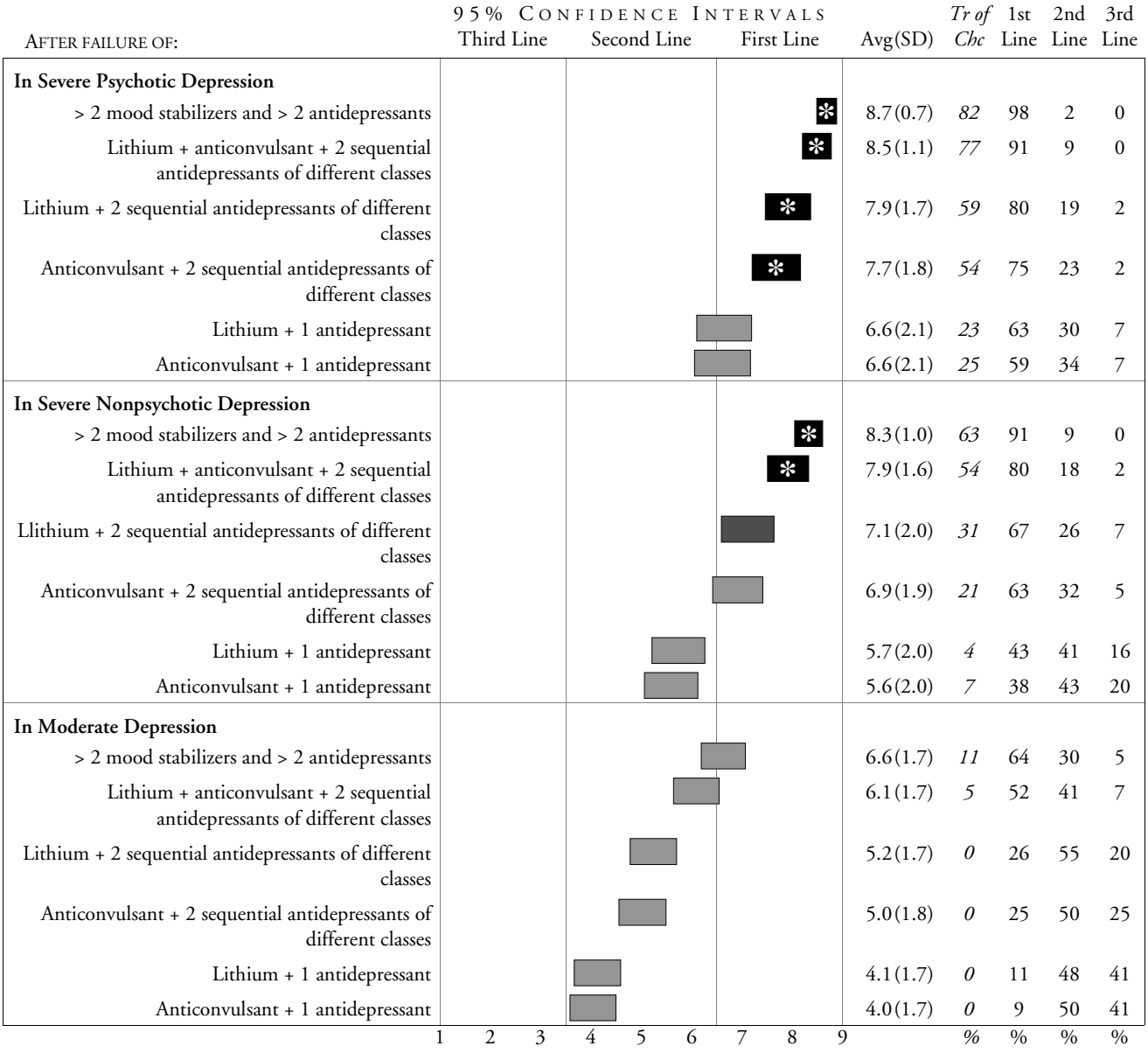
INITIAL MOOD STABILIZER WAS:	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Divalproex						
Lithium		8.7(0.6)	*71*	98	2	0
Lamotrigine		7.3(1.7)	*32*	73	23	4
Carbamazepine		6.2(1.6)	*9*	44	51	6
Gabapentin		5.4(2.1)	*11*	27	52	21
Lithium						
Divalproex		7.8(1.4)	*43*	84	16	0
Lamotrigine		7.8(1.4)	*45*	82	16	2
Carbamazepine		7.1(1.5)	*26*	60	40	0
Gabapentin		5.3(2.1)	*9*	27	50	23
Carbamazepine						
Lithium		8.4(1.0)	*59*	96	4	0
Lamotrigine		7.5(1.5)	*32*	77	20	4
Divalproex		7.3(1.7)	*29*	71	26	4
Gabapentin		5.3(1.9)	*5*	23	57	20
Lamotrigine						
Lithium		8.4(1.4)	*68*	93	4	4
Divalproex		6.8(1.7)	*20*	61	38	2
Carbamazepine		6.4(1.6)	*11*	47	49	4
Gabapentin		5.2(2.0)	*4*	25	50	25
Gabapentin						
Lithium		8.4(1.2)	*61*	93	6	2
Divalproex		7.4(1.5)	*29*	75	26	0
Lamotrigine		7.2(1.9)	*31*	75	20	6
Carbamazepine		6.2(1.4)	*6*	38	62	0
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

26 **Bipolar depression with psychotic features, inadequate response: choice of next antipsychotic.** In the case of psychotic depression, assume you have prescribed an antipsychotic plus a mood stabilizer and an antidepressant, but the patient has had little or no response and you have decided to change the antipsychotic regimen. Depending on the initial class of antipsychotic you were using, please rate each of the following options for the next choice. Would you pick another drug in the same class, switch to the other class, or combine classes?



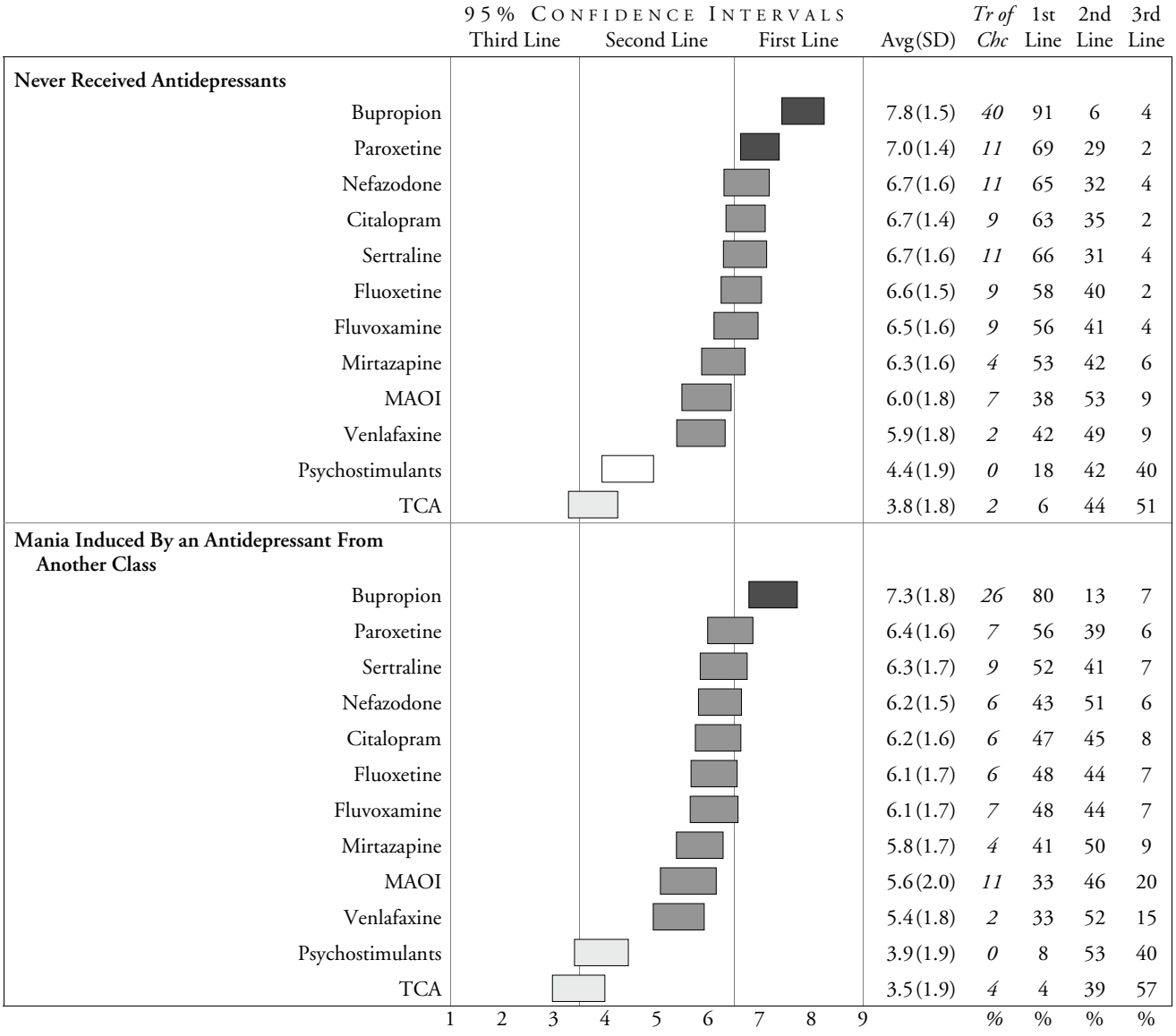
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
If Initial Class Was Conventional Antipsychotic					
An atypical antipsychotic other than clozapine	8.5(1.0)	*71*	95	5	0
Clozapine	5.8(2.0)	*11*	36	50	14
Combine atypical with conventional antipsychotic	5.0(1.9)	*2*	25	48	27
A conventional antipsychotic	4.5(1.8)	*0*	14	54	32
If Initial Class Was Atypical Antipsychotic					
An atypical antipsychotic other than clozapine	7.5(1.7)	*39*	73	23	4
A conventional antipsychotic	6.6(2.0)	*25*	54	39	7
Clozapine	6.0(2.3)	*18*	43	39	18
Combine atypical with conventional antipsychotic	5.2(2.1)	*7*	30	43	27
		%	%	%	%

27 **Threshold for electroconvulsive therapy (ECT) in treatment-refractory bipolar depression.** Please rate the appropriateness of recommending ECT as a preferred treatment for refractory bipolar depression in each of the following situations. Assume that patient has had adequate doses and durations of the medications shown. Also assume that the patient is not in immediate danger of suicide or medical compromise and that antidepressants do not cause this patient to cycle.



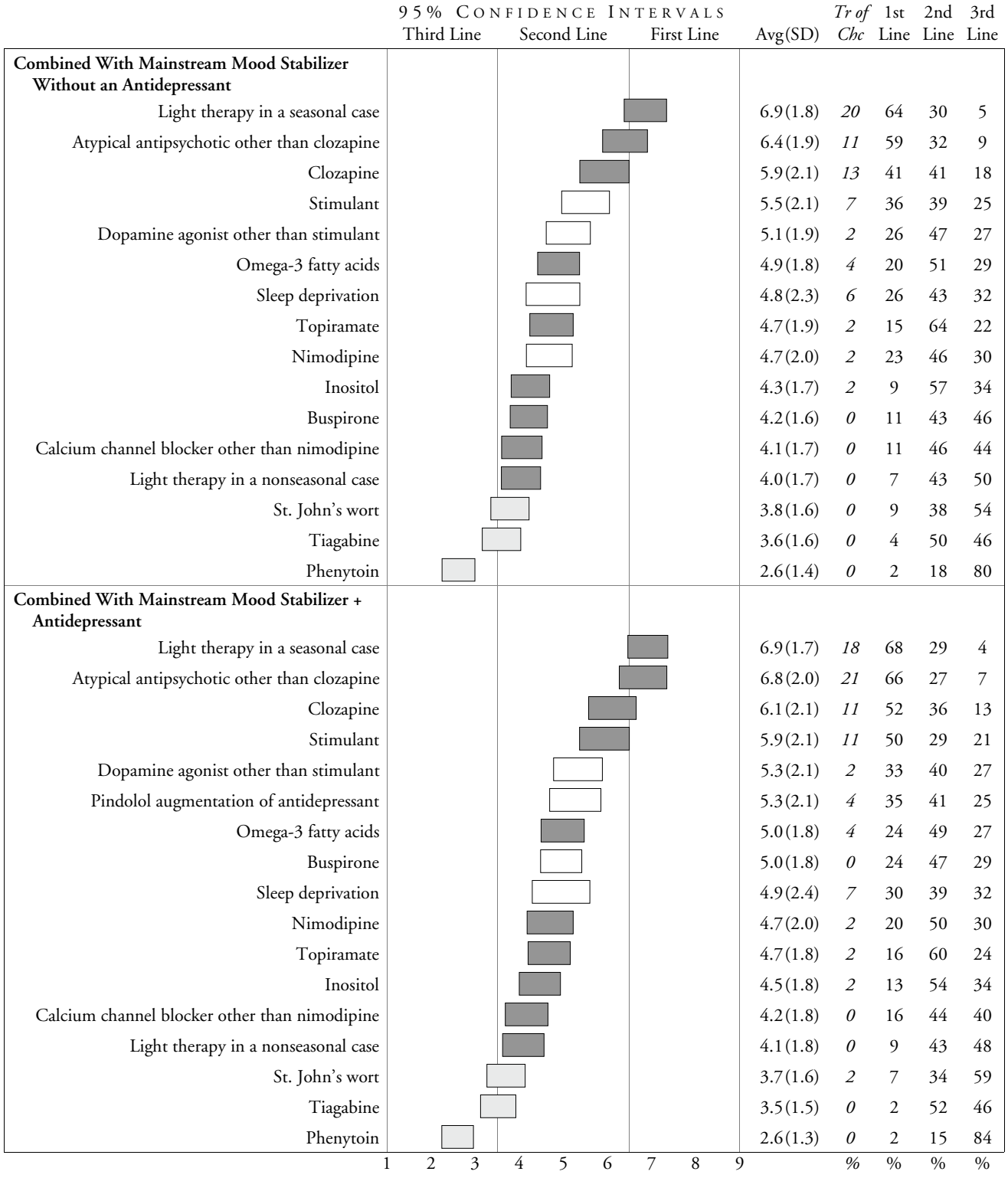
AFTER FAILURE OF:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
In Severe Psychotic Depression					
> 2 mood stabilizers and > 2 antidepressants	8.7(0.7)	*82*	98	2	0
Lithium + anticonvulsant + 2 sequential antidepressants of different classes	8.5(1.1)	*77*	91	9	0
Lithium + 2 sequential antidepressants of different classes	7.9(1.7)	*59*	80	19	2
Anticonvulsant + 2 sequential antidepressants of different classes	7.7(1.8)	*54*	75	23	2
Lithium + 1 antidepressant	6.6(2.1)	*23*	63	30	7
Anticonvulsant + 1 antidepressant	6.6(2.1)	*25*	59	34	7
In Severe Nonpsychotic Depression					
> 2 mood stabilizers and > 2 antidepressants	8.3(1.0)	*63*	91	9	0
Lithium + anticonvulsant + 2 sequential antidepressants of different classes	7.9(1.6)	*54*	80	18	2
Llithium + 2 sequential antidepressants of different classes	7.1(2.0)	*31*	67	26	7
Anticonvulsant + 2 sequential antidepressants of different classes	6.9(1.9)	*21*	63	32	5
Lithium + 1 antidepressant	5.7(2.0)	*4*	43	41	16
Anticonvulsant + 1 antidepressant	5.6(2.0)	*7*	38	43	20
In Moderate Depression					
> 2 mood stabilizers and > 2 antidepressants	6.6(1.7)	*11*	64	30	5
Lithium + anticonvulsant + 2 sequential antidepressants of different classes	6.1(1.7)	*5*	52	41	7
Lithium + 2 sequential antidepressants of different classes	5.2(1.7)	*0*	26	55	20
Anticonvulsant + 2 sequential antidepressants of different classes	5.0(1.8)	*0*	25	50	25
Lithium + 1 antidepressant	4.1(1.7)	*0*	11	48	41
Anticonvulsant + 1 antidepressant	4.0(1.7)	*0*	9	50	41
		%	%	%	%

28 **Antidepressants less likely to precipitate mania.** Please rate the following medications in terms of the likelihood of not precipitating a manic episode in a bipolar I patient. Assume the patient is currently depressed, is receiving a mood stabilizer, and has not had a recent manic episode. Please consider 2 situations: 1) a patient who has never received an antidepressant, and 2) a patient who had a prior episode of mania induced by an antidepressant from a class other than the option being considered, while on a mood stabilizer.



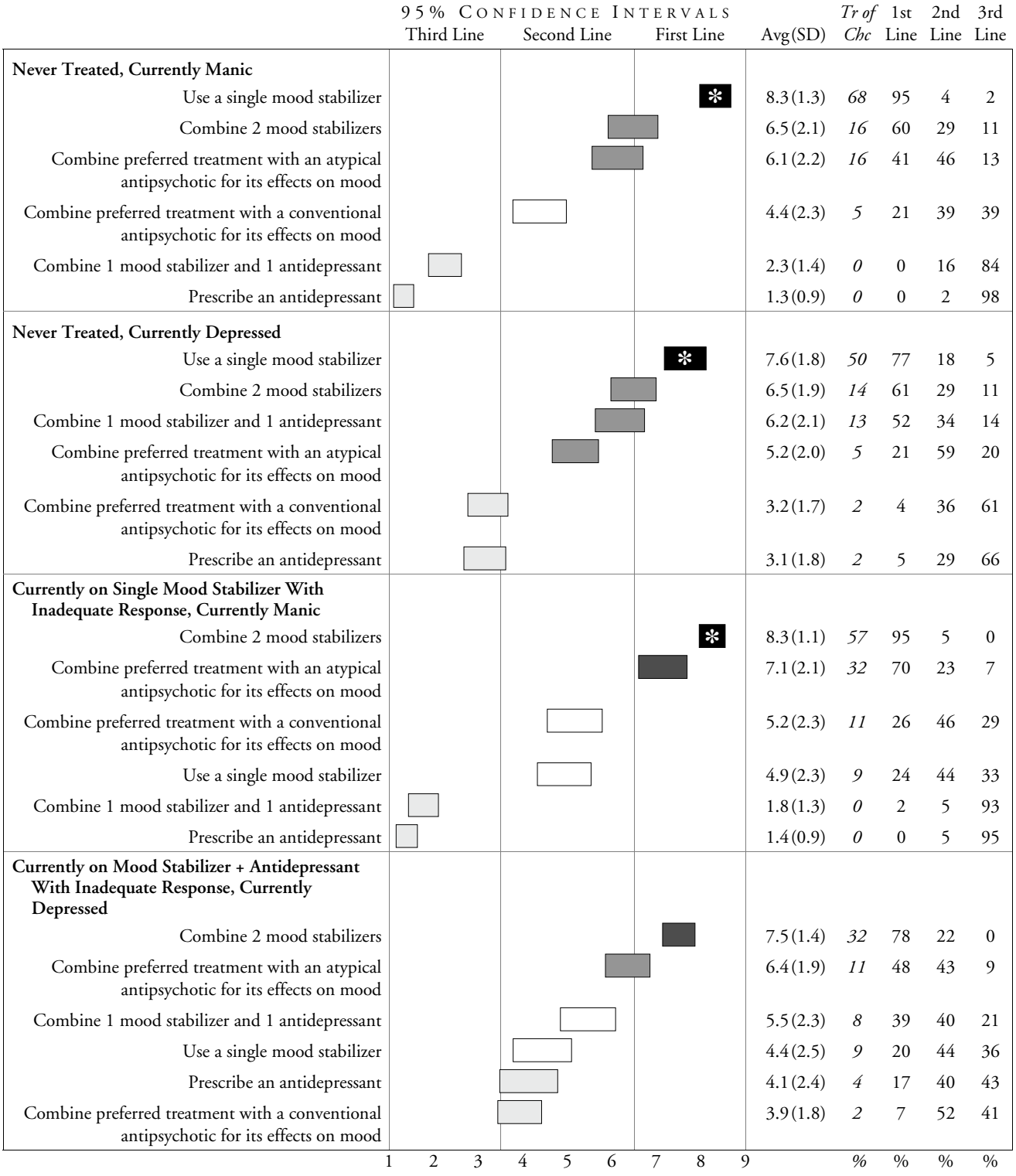
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Never Received Antidepressants					
Bupropion	7.8(1.5)	*40*	91	6	4
Paroxetine	7.0(1.4)	*11*	69	29	2
Nefazodone	6.7(1.6)	*11*	65	32	4
Citalopram	6.7(1.4)	*9*	63	35	2
Sertraline	6.7(1.6)	*11*	66	31	4
Fluoxetine	6.6(1.5)	*9*	58	40	2
Fluvoxamine	6.5(1.6)	*9*	56	41	4
Mirtazapine	6.3(1.6)	*4*	53	42	6
MAOI	6.0(1.8)	*7*	38	53	9
Venlafaxine	5.9(1.8)	*2*	42	49	9
Psychostimulants	4.4(1.9)	*0*	18	42	40
TCA	3.8(1.8)	*2*	6	44	51
Mania Induced By an Antidepressant From Another Class					
Bupropion	7.3(1.8)	*26*	80	13	7
Paroxetine	6.4(1.6)	*7*	56	39	6
Sertraline	6.3(1.7)	*9*	52	41	7
Nefazodone	6.2(1.5)	*6*	43	51	6
Citalopram	6.2(1.6)	*6*	47	45	8
Fluoxetine	6.1(1.7)	*6*	48	44	7
Fluvoxamine	6.1(1.7)	*7*	48	44	7
Mirtazapine	5.8(1.7)	*4*	41	50	9
MAOI	5.6(2.0)	*11*	33	46	20
Venlafaxine	5.4(1.8)	*2*	33	52	15
Psychostimulants	3.9(1.9)	*0*	8	53	40
TCA	3.5(1.9)	*4*	4	39	57
		%	%	%	%

29 **Novel approaches to treatment refractory bipolar depression.** Suppose you have run the gamut of various combinations of "mainstream" mood stabilizers, with and without a wide range of antidepressants augmented with thyroid, and that ECT is not an option at present. Rapid cycling, substance use, and psychosocial stress are not considered factors. Please rate each of the following alternatives as options to combine with a mood stabilizer, with or without a standard antidepressant.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Combined With Mainstream Mood Stabilizer Without an Antidepressant					
Light therapy in a seasonal case	6.9(1.8)	*20*	64	30	5
Atypical antipsychotic other than clozapine	6.4(1.9)	*11*	59	32	9
Clozapine	5.9(2.1)	*13*	41	41	18
Stimulant	5.5(2.1)	*7*	36	39	25
Dopamine agonist other than stimulant	5.1(1.9)	*2*	26	47	27
Omega-3 fatty acids	4.9(1.8)	*4*	20	51	29
Sleep deprivation	4.8(2.3)	*6*	26	43	32
Topiramate	4.7(1.9)	*2*	15	64	22
Nimodipine	4.7(2.0)	*2*	23	46	30
Inositol	4.3(1.7)	*2*	9	57	34
Buspirone	4.2(1.6)	*0*	11	43	46
Calcium channel blocker other than nimodipine	4.1(1.7)	*0*	11	46	44
Light therapy in a nonseasonal case	4.0(1.7)	*0*	7	43	50
St. John's wort	3.8(1.6)	*0*	9	38	54
Tiagabine	3.6(1.6)	*0*	4	50	46
Phenytoin	2.6(1.4)	*0*	2	18	80
Combined With Mainstream Mood Stabilizer + Antidepressant					
Light therapy in a seasonal case	6.9(1.7)	*18*	68	29	4
Atypical antipsychotic other than clozapine	6.8(2.0)	*21*	66	27	7
Clozapine	6.1(2.1)	*11*	52	36	13
Stimulant	5.9(2.1)	*11*	50	29	21
Dopamine agonist other than stimulant	5.3(2.1)	*2*	33	40	27
Pindolol augmentation of antidepressant	5.3(2.1)	*4*	35	41	25
Omega-3 fatty acids	5.0(1.8)	*4*	24	49	27
Buspirone	5.0(1.8)	*0*	24	47	29
Sleep deprivation	4.9(2.4)	*7*	30	39	32
Nimodipine	4.7(2.0)	*2*	20	50	30
Topiramate	4.7(1.8)	*2*	16	60	24
Inositol	4.5(1.8)	*2*	13	54	34
Calcium channel blocker other than nimodipine	4.2(1.8)	*0*	16	44	40
Light therapy in a nonseasonal case	4.1(1.8)	*0*	9	43	48
St. John's wort	3.7(1.6)	*2*	7	34	59
Tiagabine	3.5(1.5)	*0*	2	52	46
Phenytoin	2.6(1.3)	*0*	2	15	84
		%	%	%	%

30 **Rapid cycling: overall strategies.** Please rate the following interventions for a patient with recently diagnosed rapid-cycling bipolar I illness, given the treatment history and current clinical state indicated. Assume that adjunctive antipsychotics and benzodiazepines are provided as needed for management of agitation or psychosis.

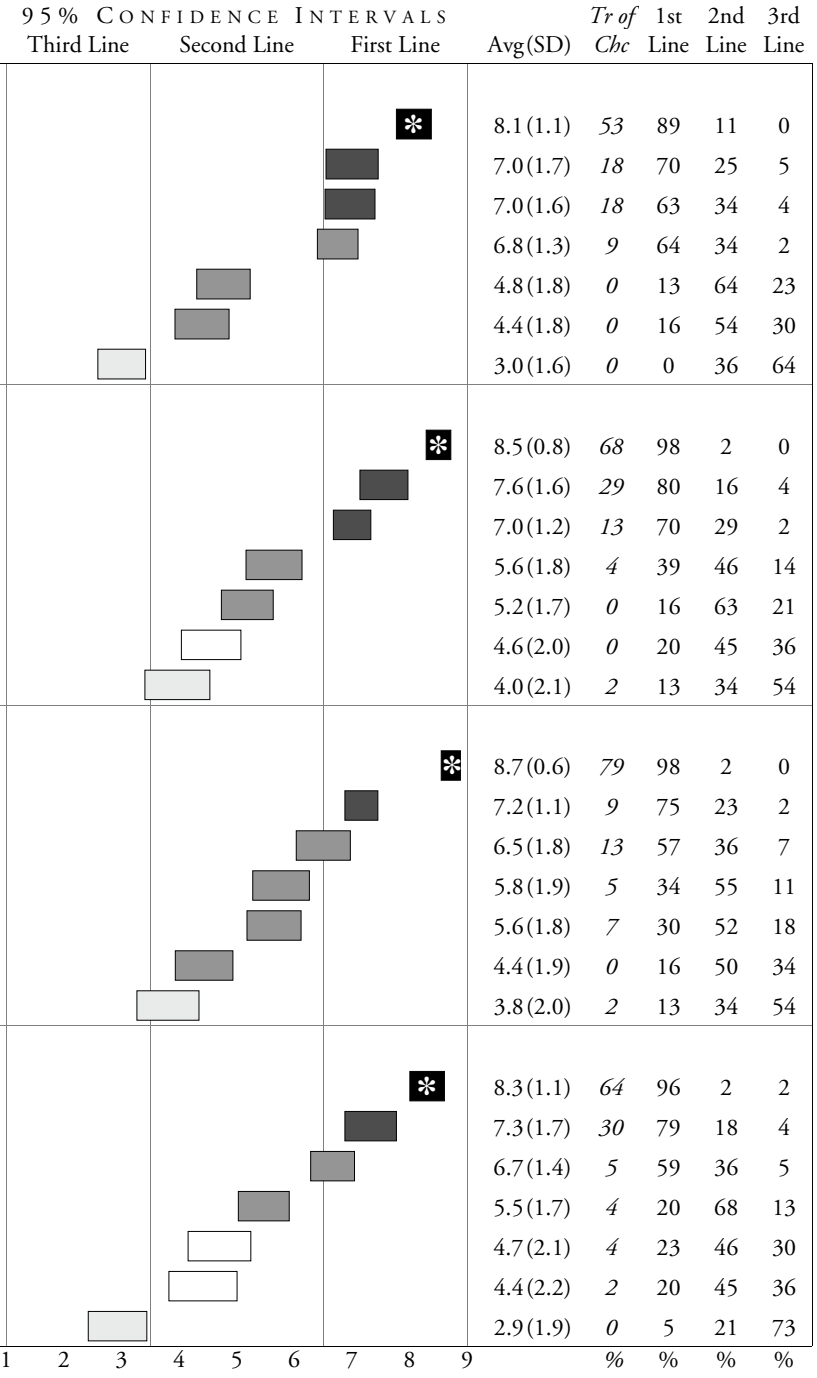


	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Never Treated, Currently Manic					
Use a single mood stabilizer	8.3 (1.3)	*68*	95	4	2
Combine 2 mood stabilizers	6.5 (2.1)	*16*	60	29	11
Combine preferred treatment with an atypical antipsychotic for its effects on mood	6.1 (2.2)	*16*	41	46	13
Combine preferred treatment with a conventional antipsychotic for its effects on mood	4.4 (2.3)	*5*	21	39	39
Combine 1 mood stabilizer and 1 antidepressant	2.3 (1.4)	*0*	0	16	84
Prescribe an antidepressant	1.3 (0.9)	*0*	0	2	98
Never Treated, Currently Depressed					
Use a single mood stabilizer	7.6 (1.8)	*50*	77	18	5
Combine 2 mood stabilizers	6.5 (1.9)	*14*	61	29	11
Combine 1 mood stabilizer and 1 antidepressant	6.2 (2.1)	*13*	52	34	14
Combine preferred treatment with an atypical antipsychotic for its effects on mood	5.2 (2.0)	*5*	21	59	20
Combine preferred treatment with a conventional antipsychotic for its effects on mood	3.2 (1.7)	*2*	4	36	61
Prescribe an antidepressant	3.1 (1.8)	*2*	5	29	66
Currently on Single Mood Stabilizer With Inadequate Response, Currently Manic					
Combine 2 mood stabilizers	8.3 (1.1)	*57*	95	5	0
Combine preferred treatment with an atypical antipsychotic for its effects on mood	7.1 (2.1)	*32*	70	23	7
Combine preferred treatment with a conventional antipsychotic for its effects on mood	5.2 (2.3)	*11*	26	46	29
Use a single mood stabilizer	4.9 (2.3)	*9*	24	44	33
Combine 1 mood stabilizer and 1 antidepressant	1.8 (1.3)	*0*	2	5	93
Prescribe an antidepressant	1.4 (0.9)	*0*	0	5	95
Currently on Mood Stabilizer + Antidepressant With Inadequate Response, Currently Depressed					
Combine 2 mood stabilizers	7.5 (1.4)	*32*	78	22	0
Combine preferred treatment with an atypical antipsychotic for its effects on mood	6.4 (1.9)	*11*	48	43	9
Combine 1 mood stabilizer and 1 antidepressant	5.5 (2.3)	*8*	39	40	21
Use a single mood stabilizer	4.4 (2.5)	*9*	20	44	36
Prescribe an antidepressant	4.1 (2.4)	*4*	17	40	43
Combine preferred treatment with a conventional antipsychotic for its effects on mood	3.9 (1.8)	*2*	7	52	41
		%	%	%	%

31 **Rapid cycling: how long to continue a successful antidepressant.** Suppose a patient has had rapid-cycling bipolar disorder for several years, dominated by long and frequent depressions. The patient has never been adequately treated and comes to you now with a major depressive episode without psychosis. You treat with several mood stabilizers and even augment with thyroid hormone, but the patient continues to be depressed. You next combine an antidepressant with a single mood stabilizer and the patient does well, remitting completely in 4 weeks in a manner you are convinced is not a placebo reaction. Please rate each of the following strategies for subsequent continuation of the antidepressant (assuming the mood stabilizer will be continued indefinitely).

WHILE CONTINUING MOOD STABILIZER:	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Bipolar I						
Taper and stop antidepressant after 1–2 months at most; resume it for future courses of short-term therapy as needed for depressive relapses		5.9(2.5)	*21*	48	30	21
Continue the antidepressant for 3–6 months then plan to taper, stopping earlier only if patient becomes manic or hypomanic		5.9(2.1)	*16*	39	46	14
Continue the antidepressant for at least 6–12 months, stopping earlier only if patient becomes manic or hypomanic		5.7(2.3)	*11*	41	34	25
Continue the antidepressant indefinitely unless patient becomes manic or hypomanic		4.7(2.7)	*11*	29	30	41
Bipolar II						
Continue the antidepressant for at least 6–12 months, stopping earlier only if patient becomes manic or hypomanic		5.9(2.4)	*14*	48	27	25
Continue the antidepressant for 3–6 months then plan to taper, stopping earlier only if patient becomes manic or hypomanic		5.8(2.1)	*14*	38	46	16
Taper and stop antidepressant after 1–2 months at most; resume it for future courses of short-term therapy as needed for depressive relapses		5.5(2.6)	*18*	43	34	23
Continue the antidepressant indefinitely unless patient becomes manic or hypomanic		5.3(2.8)	*21*	36	30	34
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

32 **Rapid cycling: mood stabilizer selection for monotherapy.** A patient with no prior treatment comes to you with a history of rapid-cycling bipolar disorder without psychosis. Assume you have decided to use a mood stabilizer in an initial attempt at monotherapy (plus adjuncts for insomnia or agitation). Please rate each of the following options, depending on the diagnosis and current phase.

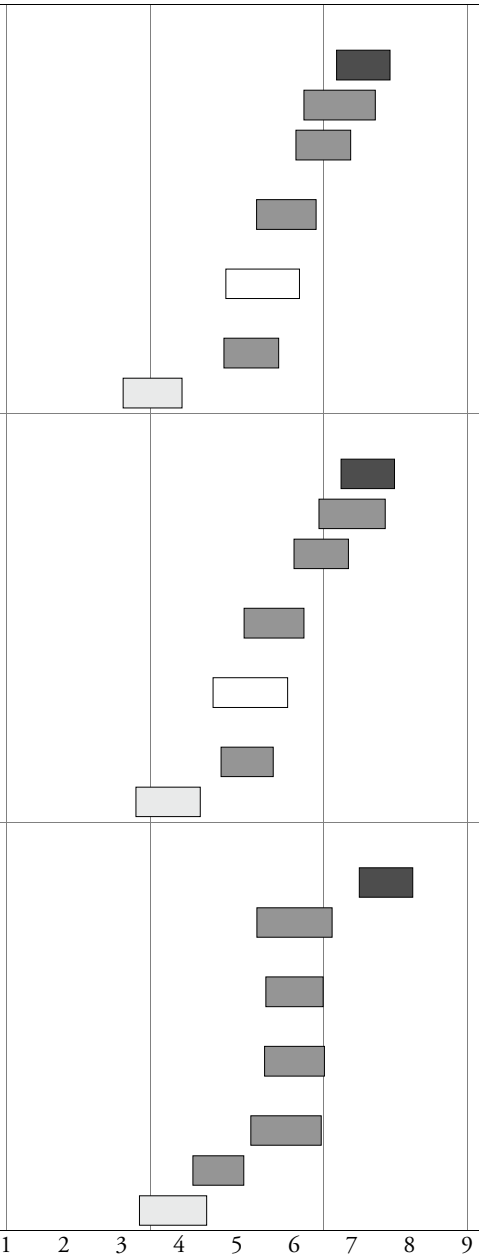


CURRENT PHASE:	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Bipolar I, Depressed					
Divalproex	8.1 (1.1)	*53*	89	11	0
Lithium	7.0 (1.7)	*18*	70	25	5
Lamotrigine	7.0 (1.6)	*18*	63	34	4
Carbamazepine	6.8 (1.3)	*9*	64	34	2
Atypical antipsychotic	4.8 (1.8)	*0*	13	64	23
Gabapentin	4.4 (1.8)	*0*	16	54	30
Conventional antipsychotic	3.0 (1.6)	*0*	0	36	64
Bipolar I, Euphoric Mania					
Divalproex	8.5 (0.8)	*68*	98	2	0
Lithium	7.6 (1.6)	*29*	80	16	4
Carbamazepine	7.0 (1.2)	*13*	70	29	2
Atypical antipsychotic	5.6 (1.8)	*4*	39	46	14
Lamotrigine	5.2 (1.7)	*0*	16	63	21
Gabapentin	4.6 (2.0)	*0*	20	45	36
Conventional antipsychotic	4.0 (2.1)	*2*	13	34	54
Bipolar I, Dysphoric or Mixed Mania					
Divalproex	8.7 (0.6)	*79*	98	2	0
Carbamazepine	7.2 (1.1)	*9*	75	23	2
Lithium	6.5 (1.8)	*13*	57	36	7
Atypical antipsychotic	5.8 (1.9)	*5*	34	55	11
Lamotrigine	5.6 (1.8)	*7*	30	52	18
Gabapentin	4.4 (1.9)	*0*	16	50	34
Conventional antipsychotic	3.8 (2.0)	*2*	13	34	54
Bipolar II, Hypomanic					
Divalproex	8.3 (1.1)	*64*	96	2	2
Lithium	7.3 (1.7)	*30*	79	18	4
Carbamazepine	6.7 (1.4)	*5*	59	36	5
Lamotrigine	5.5 (1.7)	*4*	20	68	13
Gabapentin	4.7 (2.1)	*4*	23	46	30
Atypical antipsychotic	4.4 (2.2)	*2*	20	45	36
Conventional antipsychotic	2.9 (1.9)	*0*	5	21	73
		%	%	%	%

33 **Rapid cycling: breakthrough mania during maintenance with carbamazepine, divalproex, or lithium.** Suppose a patient has had a rapid-cycling bipolar I course off and on for 5 years. A "mainstream" mood stabilizer regimen appeared effective at first but, despite complete adherence to maximal doses, rapid-cycling breakthroughs of mania or hypomania have always resumed within 3 to 6 months, requiring a few weeks of adjunctive antipsychotics or benzodiazepines. Depressions have been well controlled, however, without the need for antidepressants. The patient now presents with mania and you decide to add another mood stabilizer with the hopes of continuing it long-term if it works during the acute phase. Please rate each of the following options as add-on therapy, depending on the current mood stabilizer (assume the use of any adjuncts you wish for insomnia or agitation).

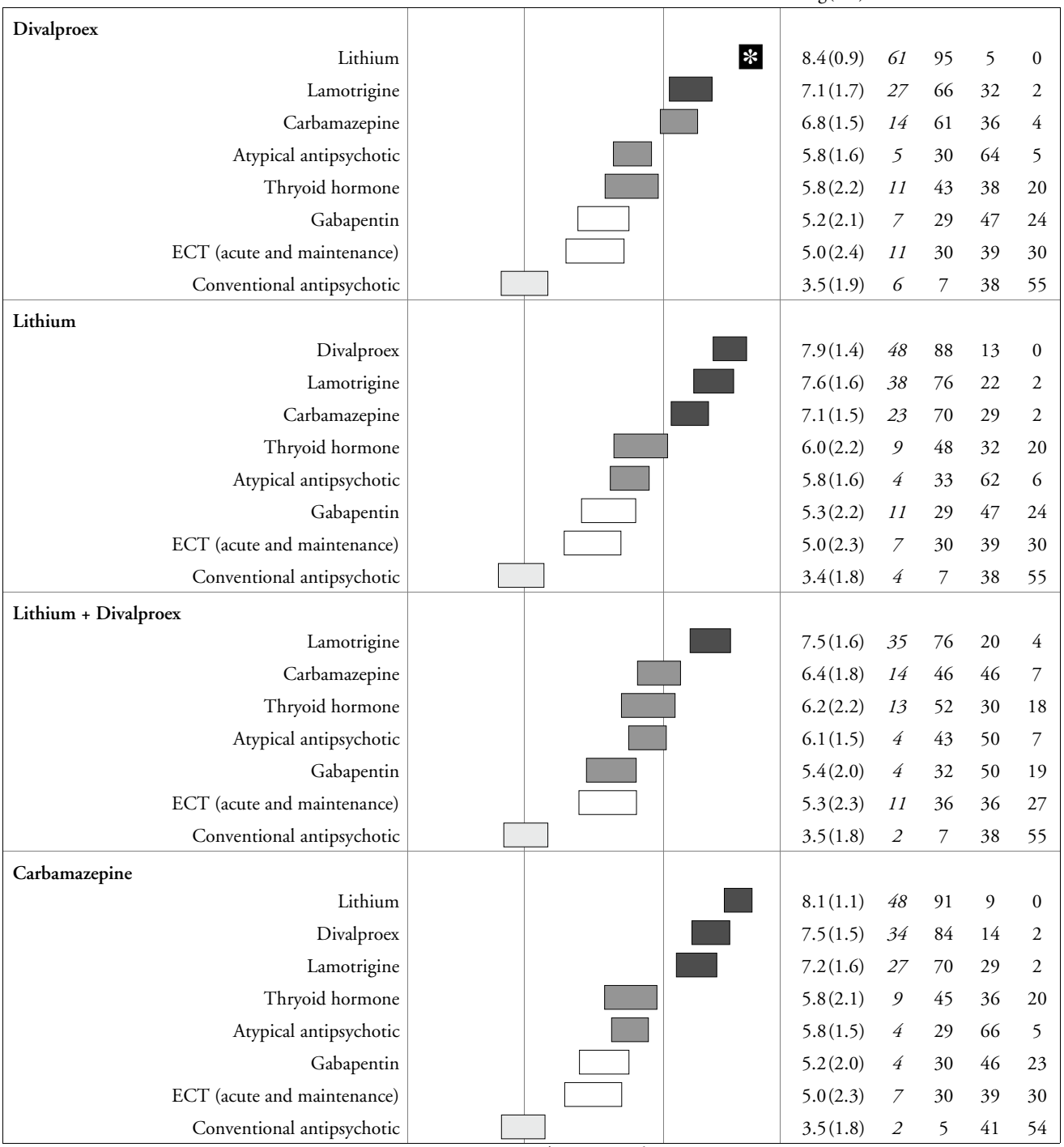
CURRENTLY MANIC WHILE TAKING:	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Carbamazepine						
Lithium		8.1(1.2)	*50*	91	7	2
Divalproex		8.0(1.3)	*47*	89	9	2
Lamotrigine		5.6(1.6)	*6*	26	66	9
Gabapentin		5.1(2.1)	*5*	27	45	29
Divalproex						
Lithium		8.5(1.1)	*70*	96	2	2
Carbamazepine		7.1(1.4)	*20*	71	27	2
Lamotrigine		5.4(1.8)	*6*	29	56	15
Gabapentin		5.2(2.0)	*5*	27	46	27
Lithium						
Divalproex		8.8(0.6)	*84*	98	2	0
Carbamazepine		7.3(1.3)	*20*	77	21	2
Lamotrigine		6.0(1.7)	*7*	40	53	7
Gabapentin		5.4(2.1)	*5*	30	45	25
Lithium + Divalproex						
Carbamazepine		7.1(1.5)	*27*	68	30	2
Lamotrigine		5.8(1.9)	*9*	42	46	13
Gabapentin		5.6(1.9)	*9*	32	55	13
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

34 **Rapid cycling: currently depressed, cycles more with SSRIs.** A bipolar I patient maintained on 1 or 2 mood stabilizers has been treated intermittently for recurrent depressions using SSRIs. In the past year, the patient switched to manic and hypomanic episodes 4 times shortly after starting an SSRI but fell back into depression after the SSRI was stopped. The patient has now been depressed for 3 months on mood stabilizer(s) alone at the maximum tolerable dose. Thryoid functions are normal. Please rate each of the following strategies based on the patient's current mood stabilizer.



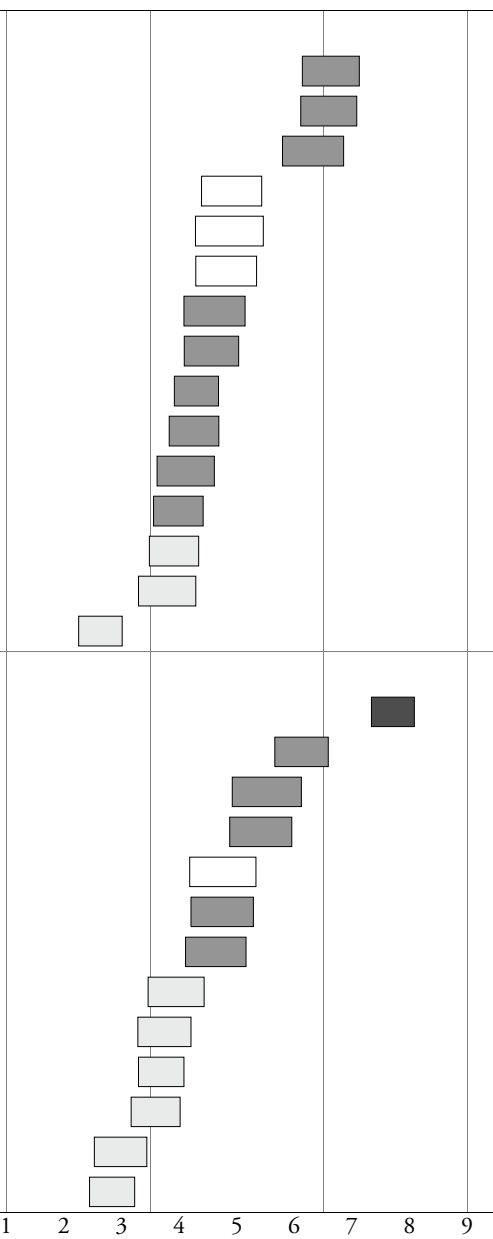
Current Regimen:	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lithium					
Add a non-SSRI antidepressant	7.2 (1.8)	*30*	70	27	4
Add another antimanic drug	6.8 (2.3)	*40*	58	29	13
Add another antimanic drug and a non-SSRI antidepressant	6.5 (1.8)	*11*	59	34	7
In addition to top-ranked changes above, add thyroid hormone	5.9 (2.0)	*7*	41	45	14
Continue current regimen and add thyroid hormone	5.5 (2.4)	*11*	39	38	23
Add another anti-manic drug and retry an SSRI	5.3 (1.8)	*4*	25	54	21
Lower doses of current mood stabilizers	3.5 (1.9)	*0*	11	36	54
Divalproex					
Add a non-SSRI antidepressant	7.3 (1.7)	*31*	76	20	4
Add another antimanic drug	7.0 (2.2)	*39*	65	26	9
Add another antimanic drug and a non-SSRI antidepressant	6.5 (1.8)	*11*	55	38	7
In addition to top-ranked changes above, add thyroid hormone	5.6 (2.0)	*5*	38	46	16
Continue current regimen and add thyroid hormone	5.2 (2.5)	*11*	38	34	29
Add another anti-manic drug and retry an SSRI	5.2 (1.7)	*4*	23	55	21
Lower doses of current mood stabilizers	3.8 (2.1)	*0*	14	36	50
Lithium + Divalproex					
Add a non-SSRI antidepressant	7.6 (1.8)	*46*	79	18	4
Continue current regimen and add thyroid hormone	6.0 (2.5)	*20*	46	34	20
Add another antimanic drug and a non-SSRI antidepressant	6.0 (1.9)	*9*	44	46	11
In addition to top-ranked changes above, add thyroid hormone	6.0 (2.0)	*7*	43	46	11
Add another antimanic drug	5.9 (2.3)	*17*	41	44	15
Add another anti-manic drug and retry an SSRI	4.7 (1.7)	*0*	16	52	32
Lower doses of current mood stabilizers	3.9 (2.2)	*2*	18	38	45
		%	%	%	%

35 **Rapid-cycling, currently depressed, cycles more with any antidepressant; selecting alternatives.** Consider a patient who has had a rapid-cycling bipolar I course off and on for several years. A "mainstream" mood stabilizer regimen appeared effective at first against both depression and mania but, despite complete adherence to maximal doses, rapid-cycling breakthroughs of depression always resumed within 6 months, requiring brief courses of antidepressants. Unfortunately, a wide variety of different antidepressants have all led to episodes of mania or hypomania in this patient. You now decide to add another mood stabilizer with the hopes of continuing it long-term if it works in the acute phase, and to avoid future antidepressants altogether. Please rate each of the following options as add-on therapy depending on the current mood stabilizer.



CURRENTLY DEPRESSED ON:	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Divalproex					
Lithium	8.4 (0.9)	*61*	95	5	0
Lamotrigine	7.1 (1.7)	*27*	66	32	2
Carbamazepine	6.8 (1.5)	*14*	61	36	4
Atypical antipsychotic	5.8 (1.6)	*5*	30	64	5
Thryoid hormone	5.8 (2.2)	*11*	43	38	20
Gabapentin	5.2 (2.1)	*7*	29	47	24
ECT (acute and maintenance)	5.0 (2.4)	*11*	30	39	30
Conventional antipsychotic	3.5 (1.9)	*6*	7	38	55
Lithium					
Divalproex	7.9 (1.4)	*48*	88	13	0
Lamotrigine	7.6 (1.6)	*38*	76	22	2
Carbamazepine	7.1 (1.5)	*23*	70	29	2
Thryoid hormone	6.0 (2.2)	*9*	48	32	20
Atypical antipsychotic	5.8 (1.6)	*4*	33	62	6
Gabapentin	5.3 (2.2)	*11*	29	47	24
ECT (acute and maintenance)	5.0 (2.3)	*7*	30	39	30
Conventional antipsychotic	3.4 (1.8)	*4*	7	38	55
Lithium + Divalproex					
Lamotrigine	7.5 (1.6)	*35*	76	20	4
Carbamazepine	6.4 (1.8)	*14*	46	46	7
Thryoid hormone	6.2 (2.2)	*13*	52	30	18
Atypical antipsychotic	6.1 (1.5)	*4*	43	50	7
Gabapentin	5.4 (2.0)	*4*	32	50	19
ECT (acute and maintenance)	5.3 (2.3)	*11*	36	36	27
Conventional antipsychotic	3.5 (1.8)	*2*	7	38	55
Carbamazepine					
Lithium	8.1 (1.1)	*48*	91	9	0
Divalproex	7.5 (1.5)	*34*	84	14	2
Lamotrigine	7.2 (1.6)	*27*	70	29	2
Thryoid hormone	5.8 (2.1)	*9*	45	36	20
Atypical antipsychotic	5.8 (1.5)	*4*	29	66	5
Gabapentin	5.2 (2.0)	*4*	30	46	23
ECT (acute and maintenance)	5.0 (2.3)	*7*	30	39	30
Conventional antipsychotic	3.5 (1.8)	*2*	5	41	54
		%	%	%	%

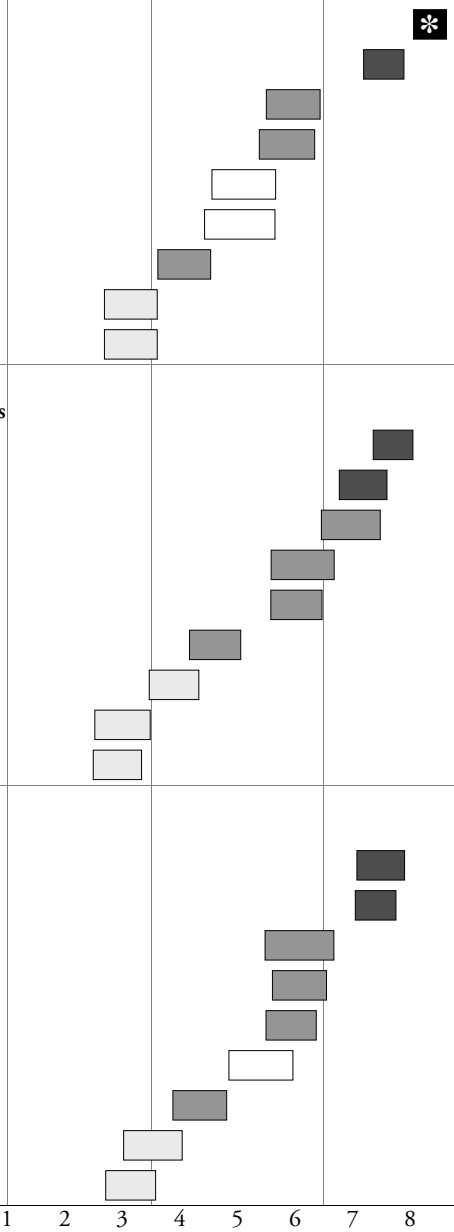
36 **Rapid cycling: alternative treatments.** Suppose that you have run the gamut of various combinations of "mainstream" mood stabilizers, adjunctive antipsychotics, and benzodiazepines, but the patient continues to have at least 4 breakthrough episodes per year involving both poles. Assume that the patient cannot tolerate antidepressants because of increased cycling. Please rate the general effectiveness of the following alternative options as add-on treatments for symptoms of depression or mania.



	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
As Add-On for Depressive Symptoms					
Thyroid hormone in some form	6.6 (1.8)	*15*	61	33	6
Light therapy in a seasonal case	6.6 (1.8)	*13*	63	30	7
Clozapine	6.3 (2.0)	*11*	53	38	9
Dopamine agonist other than stimulant	4.9 (2.0)	*0*	24	46	31
Sleep deprivation	4.9 (2.2)	*2*	30	36	34
Omega-3 fatty acids	4.8 (2.0)	*4*	20	46	33
Nimodipine	4.6 (2.0)	*2*	20	50	30
Topiramate	4.6 (1.7)	*0*	12	69	19
Inositol	4.3 (1.4)	*0*	9	57	33
Buspirone	4.3 (1.6)	*0*	9	51	40
Light therapy in a nonseasonal case	4.1 (1.8)	*0*	13	41	46
Calcium channel blocker other than nimodipine	4.0 (1.6)	*2*	4	55	42
St. John's wort	3.9 (1.6)	*0*	6	52	43
Tiagabine	3.8 (1.8)	*0*	8	52	40
Phenytoin	2.6 (1.4)	*0*	2	20	78
As Add-On for Manic Symptoms					
Clozapine	7.7 (1.4)	*38*	82	16	2
Topiramate	6.1 (1.7)	*8*	40	56	4
Thyroid hormone in some form	5.5 (2.2)	*8*	38	44	18
Nimodipine	5.4 (2.0)	*6*	38	49	13
Omega-3 fatty acids	4.8 (2.1)	*4*	21	45	34
Calcium channel blocker other than nimodipine	4.8 (2.0)	*2*	24	51	26
Tiagabine	4.6 (1.9)	*0*	18	55	27
Cholinesterase inhibitor	3.9 (1.8)	*0*	9	43	47
Choline	3.7 (1.7)	*0*	9	44	46
Inositol	3.7 (1.5)	*0*	6	43	52
Beta blocker	3.6 (1.5)	*0*	4	41	55
Phenytoin	3.0 (1.7)	*0*	4	28	69
Dopamine agonist other than stimulant	2.8 (1.5)	*0*	2	28	70
		%	%	%	%

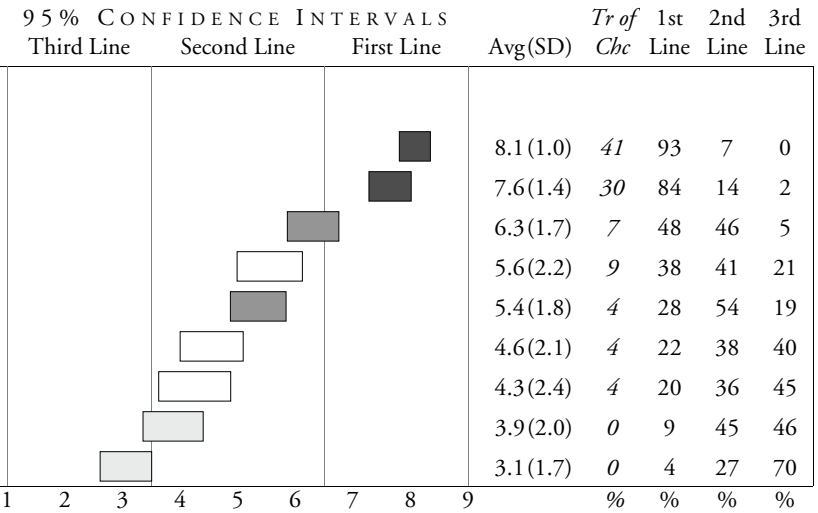
37 **Starting the right medication for a previously misdiagnosed patient with chronic bipolar disorder.** Many patients with bipolar disorder are misdiagnosed for an average of 8 years. Suppose a patient comes to you for consultation 1 month after stabilization from an acute psychiatric exacerbation (e.g., with antidepressants or antipsychotics alone) but having never received a mood stabilizer. You now diagnose the patient as bipolar and recommend a mood stabilizer and perhaps other medications. Please rate each option for the vignettes presented below.

FORMER DIAGNOSIS NEW DIAGNOSIS	95% CONFIDENCE INTERVALS Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Unipolar Depression **Bipolar I, recently depressed**						
Lithium alone		8.3(1.1)	*61*	96	2	2
Divalproex alone		7.5(1.3)	*30*	80	18	2
Carbamazepine alone		6.0(1.8)	*11*	34	61	5
Lamotrigine alone		5.9(1.8)	*7*	36	54	11
Combine 2 top-ranked mood stabilizers		5.1(2.1)	*5*	29	48	23
Include an antidepressant in the initial plan		5.0(2.3)	*7*	29	41	30
Gabapentin alone		4.1(1.7)	*0*	11	46	44
Include an antipsychotic in the initial plan		3.2(1.7)	*0*	4	33	64
Calcium channel blocker alone		3.1(1.7)	*2*	4	29	68
Schizophrenia **Bipolar I, recently manic with psychotic features**						
Divalproex alone		7.7(1.3)	*34*	84	16	0
Lithium alone		7.2(1.6)	*25*	68	29	4
Include an antipsychotic in the initial plan*		7.0(1.9)	*29*	68	27	5
Combine 2 top-ranked mood stabilizers		6.1(2.1)	*15*	47	38	15
Carbamazepine alone		6.0(1.7)	*7*	40	55	6
Lamotrigine alone		4.6(1.7)	*0*	11	59	30
Gabapentin alone		3.9(1.6)	*0*	7	45	48
Include an antidepressant in the initial plan		3.0(1.8)	*0*	4	29	68
Calcium channel blocker alone		2.9(1.6)	*0*	2	27	71
Borderline Personality Disorder + Dysthymia **Bipolar II, recently depressed**						
Divalproex alone		7.5(1.6)	*38*	80	16	4
Lithium alone		7.4(1.3)	*23*	86	13	2
Include an antidepressant in the initial plan		6.1(2.3)	*16*	55	27	18
Lamotrigine alone		6.1(1.8)	*11*	41	52	7
Carbamazepine alone		5.9(1.6)	*7*	34	59	7
Combine 2 top-ranked mood stabilizers		5.4(2.1)	*4*	33	44	24
Gabapentin alone		4.3(1.8)	*0*	14	45	41
Include an antipsychotic in the initial plan		3.5(1.9)	*0*	6	42	53
Calcium channel blocker alone		3.1(1.6)	*0*	0	34	66
	1 2 3 4 5 6 7 8 9		*%*	%	%	%



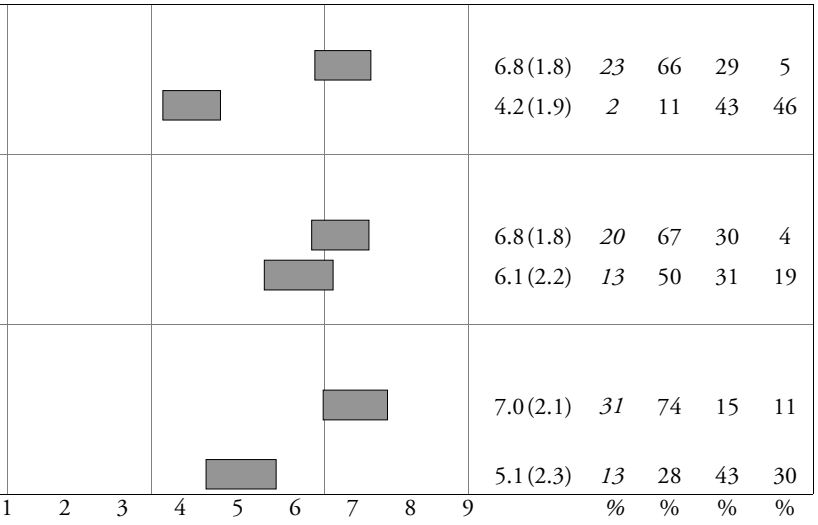
*One-way ANOVA found no difference between this option and the 2 first-line options ($F = 2.989$, $P = 0.53$).

37 Starting the right medication for a previously misdiagnosed patient with chronic bipolar disorder, *continued*



Former Diagnosis / New Diagnosis	95% Confidence Intervals: Third Line	Second Line	First Line	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
ADHD								
Bipolar II, recently hypomanic								
Divalproex alone				8.1 (1.0)	*41*	93	7	0
Lithium alone				7.6 (1.4)	*30*	84	14	2
Carbamazepine alone				6.3 (1.7)	*7*	48	46	5
Combine 2 top-ranked mood stabilizers				5.6 (2.2)	*9*	38	41	21
Lamotrigine alone				5.4 (1.8)	*4*	28	54	19
Gabapentin alone				4.6 (2.1)	*4*	22	38	40
Include an antidepressant in the initial plan				4.3 (2.4)	*4*	20	36	45
Include an antipsychotic in the initial plan				3.9 (2.0)	*0*	9	45	46
Calcium channel blocker alone				3.1 (1.7)	*0*	4	27	70
	1 2 3 4 5 6 7 8 9				%	%	%	%

38 **Thyroid hormone.** Thyroid hormone is thought to help stabilize some bipolar patients. Please rate the following strategies for its use in the following situations. AD = antidepressant, MS = mood stabilizer.

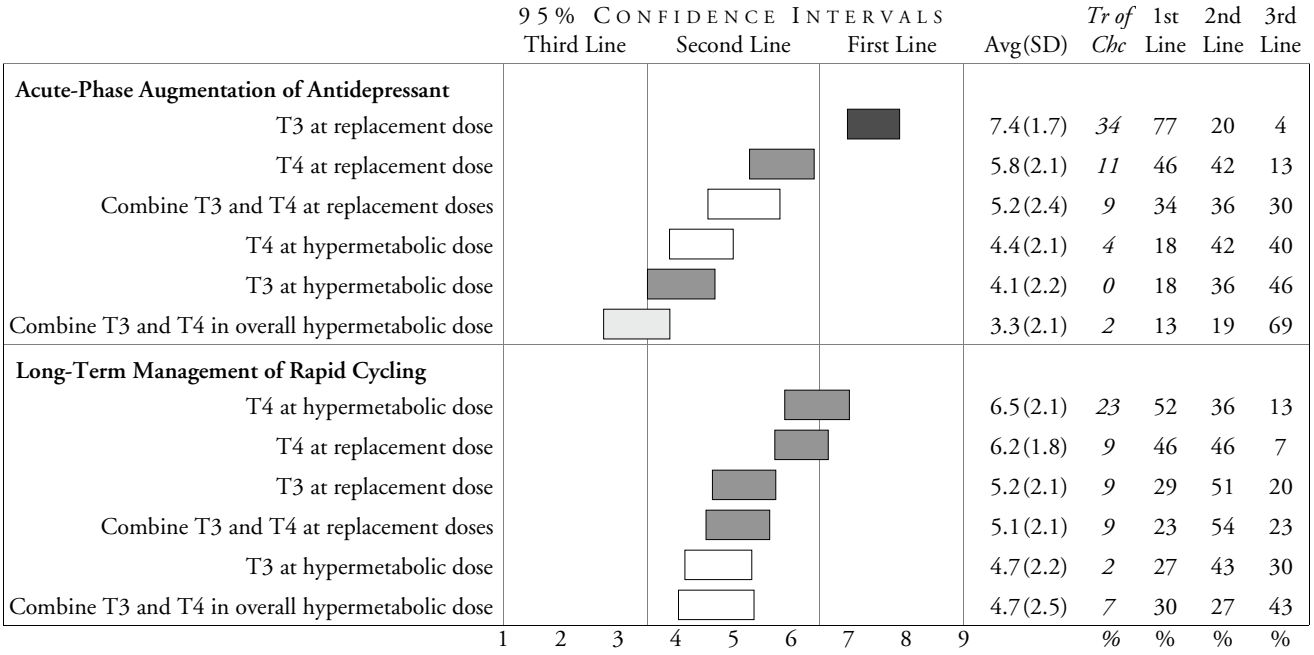


95% Confidence Intervals: Third Line	Second Line	First Line	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Non-rapid cycling, inadequate response to AD							
Combine thyroid hormone with AD and MS			6.8 (1.8)	*23*	66	29	5
Discontinue or do not initiate AD; use thyroid hormone only + MS			4.2 (1.9)	*2*	11	43	46
Rapid cycling with frequent depression; mania is suppressed with MS							
Combine thyroid hormone with AD and MS			6.8 (1.8)	*20*	67	30	4
Discontinue or do not initiate AD; use thyroid hormone only + MS			6.1 (2.2)	*13*	50	31	19
Rapid cycling, depressed on MS alone, (hypo)manic on AD							
Discontinue or do not initiate AD; use thyroid hormone only + MS			7.0 (2.1)	*31*	74	15	11
Combine thyroid hormone with AD and MS			5.1 (2.3)	*13*	28	43	30
1 2 3 4 5 6 7 8 9				%	%	%	%

Initial trial to assess efficacy	Minimum weeks Avg (SD)	Maximum weeks Avg (SD)
Non-rapid cycling	3.9 (2.7)	9.6 (7.9)
Rapid cycling with frequent depression	4.6 (3.1)	11.1 (8.4)
Rapid cycling with depression on MS and hypomania on AD	4.4 (3.0)	10.9 (8.1)

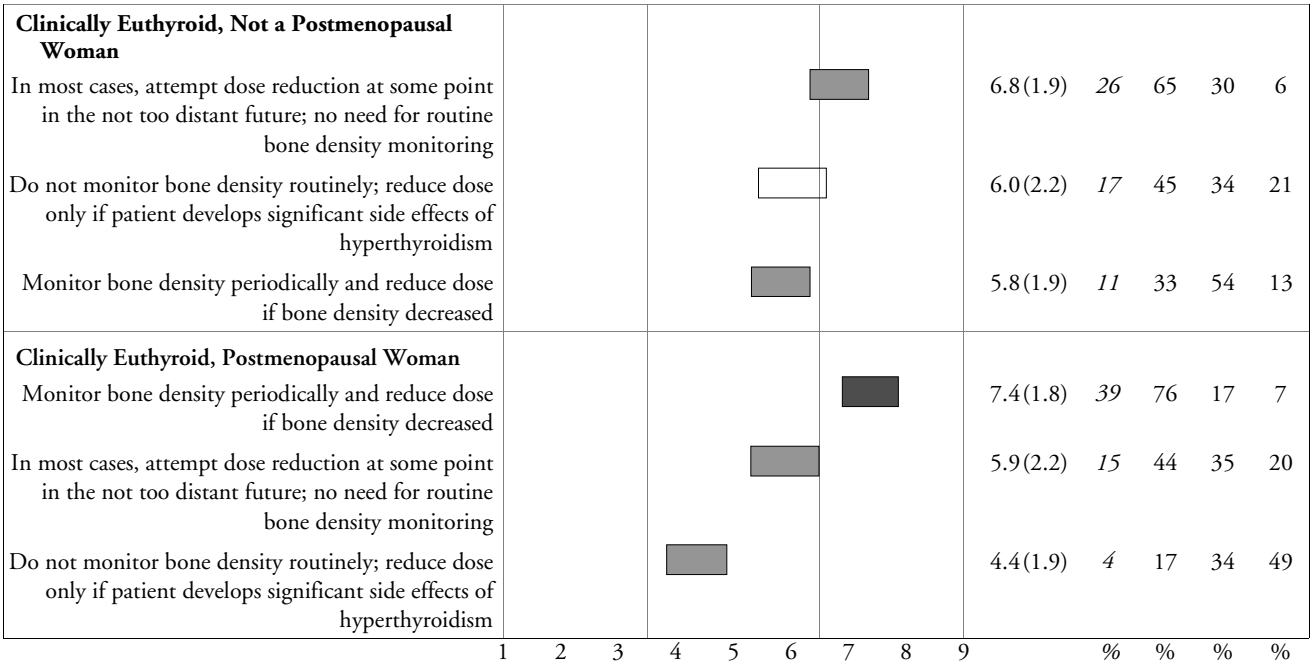
If effective, before tapering	Minimum months Avg (SD)	Maximum months Avg (SD)	Indefinitely %
Non-rapid cycling	4.2 (3.0)	9.2 (5.8)	59.3
Rapid cycling with frequent depression	6.2 (5.4)	11.9 (8.6)	75.9
Rapid cycling with depression on MS and hypomania on AD	6.2 (5.3)	12.3 (9.1)	79.6

39 **Thryoid hormone: forms and dosing.** Please rate the following forms and dosing strategies of thyroid hormone for each use.



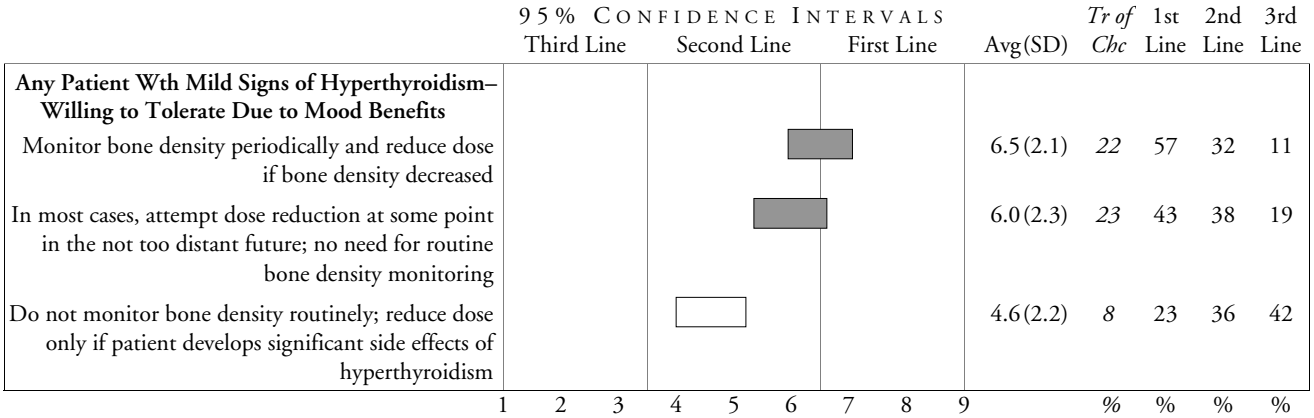
	95% Confidence Intervals Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Acute-Phase Augmentation of Antidepressant						
T3 at replacement dose		7.4(1.7)	*34*	77	20	4
T4 at replacement dose		5.8(2.1)	*11*	46	42	13
Combine T3 and T4 at replacement doses		5.2(2.4)	*9*	34	36	30
T4 at hypermetabolic dose		4.4(2.1)	*4*	18	42	40
T3 at hypermetabolic dose		4.1(2.2)	*0*	18	36	46
Combine T3 and T4 in overall hypermetabolic dose		3.3(2.1)	*2*	13	19	69
Long-Term Management of Rapid Cycling						
T4 at hypermetabolic dose		6.5(2.1)	*23*	52	36	13
T4 at replacement dose		6.2(1.8)	*9*	46	46	7
T3 at replacement dose		5.2(2.1)	*9*	29	51	20
Combine T3 and T4 at replacement doses		5.1(2.1)	*9*	23	54	23
T3 at hypermetabolic dose		4.7(2.2)	*2*	27	43	30
Combine T3 and T4 in overall hypermetabolic dose		4.7(2.5)	*7*	30	27	43
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

40 The **safety of long-term thyroid stimulating hormone (TSH) suppression** is controversial, in part due to concerns about effects on bone density. Assume that a patient with severe bipolar disorder improves markedly on hypermetabolic doses of thyroid hormone. Please rate the appropriateness of each of the following monitoring and dosing strategies depending on demographics and the presence or absence of thyroid side effects.



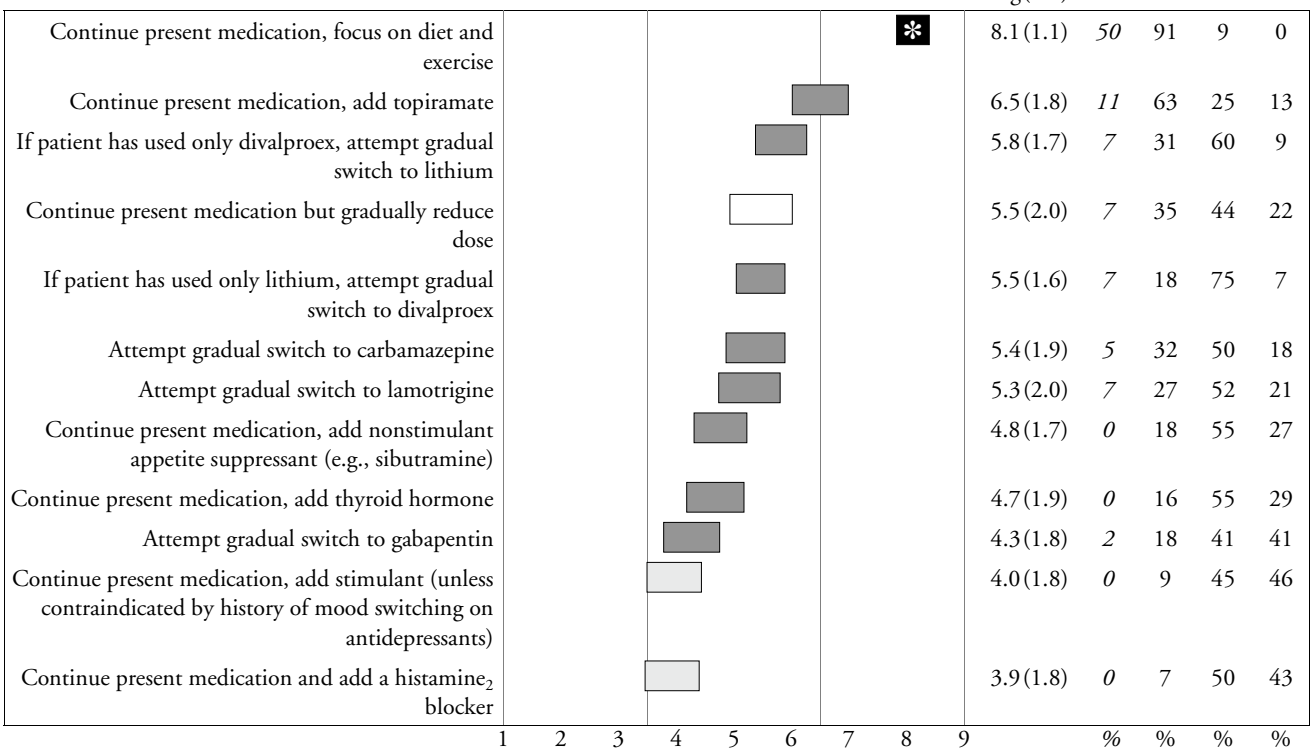
	95% Confidence Intervals Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Clinically Euthyroid, Not a Postmenopausal Woman						
In most cases, attempt dose reduction at some point in the not too distant future; no need for routine bone density monitoring		6.8(1.9)	*26*	65	30	6
Do not monitor bone density routinely; reduce dose only if patient develops significant side effects of hyperthyroidism		6.0(2.2)	*17*	45	34	21
Monitor bone density periodically and reduce dose if bone density decreased		5.8(1.9)	*11*	33	54	13
Clinically Euthyroid, Postmenopausal Woman						
Monitor bone density periodically and reduce dose if bone density decreased		7.4(1.8)	*39*	76	17	7
In most cases, attempt dose reduction at some point in the not too distant future; no need for routine bone density monitoring		5.9(2.2)	*15*	44	35	20
Do not monitor bone density routinely; reduce dose only if patient develops significant side effects of hyperthyroidism		4.4(1.9)	*4*	17	34	49
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

40 Safety of long-term thyroid stimulating hormone (TSH) suppression, *continued*



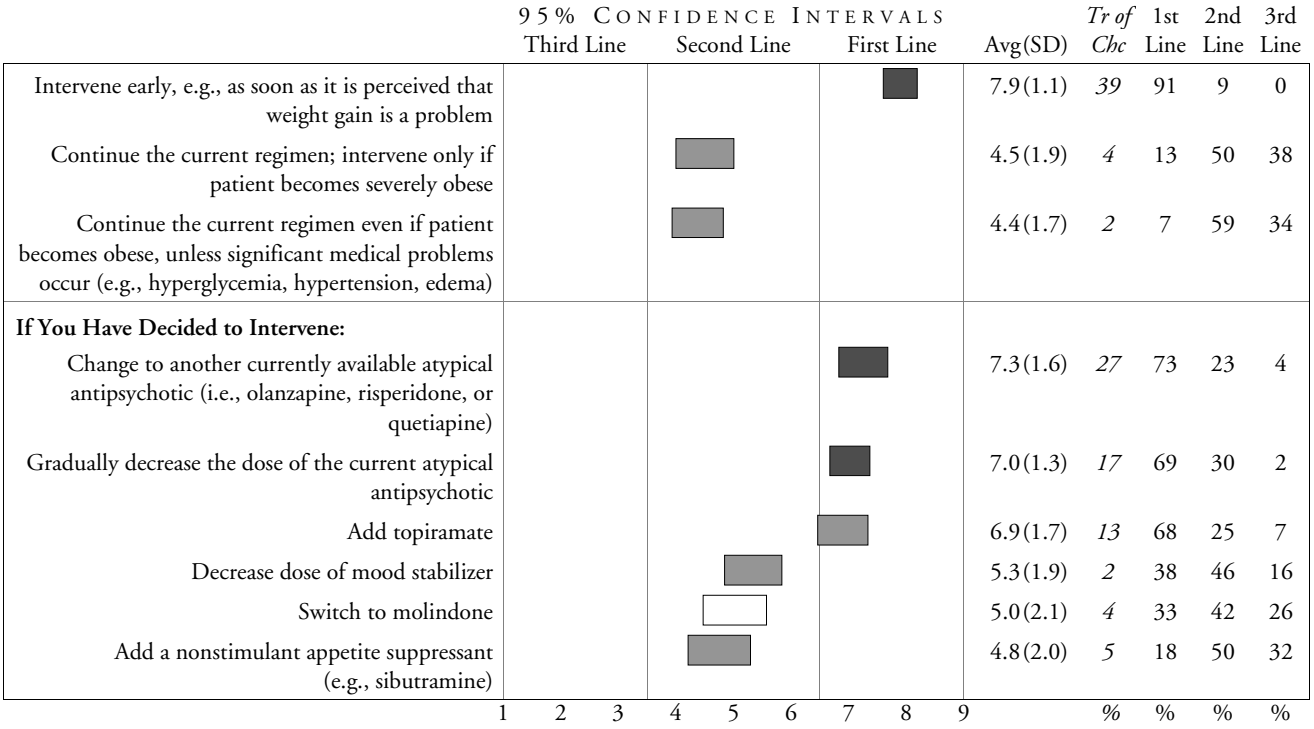
	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Any Patient Wth Mild Signs of Hyperthyroidism–Willing to Tolerate Due to Mood Benefits					
Monitor bone density periodically and reduce dose if bone density decreased	6.5 (2.1)	*22*	57	32	11
In most cases, attempt dose reduction at some point in the not too distant future; no need for routine bone density monitoring	6.0 (2.3)	*23*	43	38	19
Do not monitor bone density routinely; reduce dose only if patient develops significant side effects of hyperthyroidism	4.6 (2.2)	*8*	23	36	42
		%	%	%	%

41 **Managing weight gain on lithium or divalproex.** Please rate each of the following options for a patient who has gained an undesirable amount of weight on long-term lithium and/or divalproex, but for whom the medication has been markedly effective for long-term mood stabilization. Assume the patient is euthyroid and in good general health and has never had other mood stabilizers.

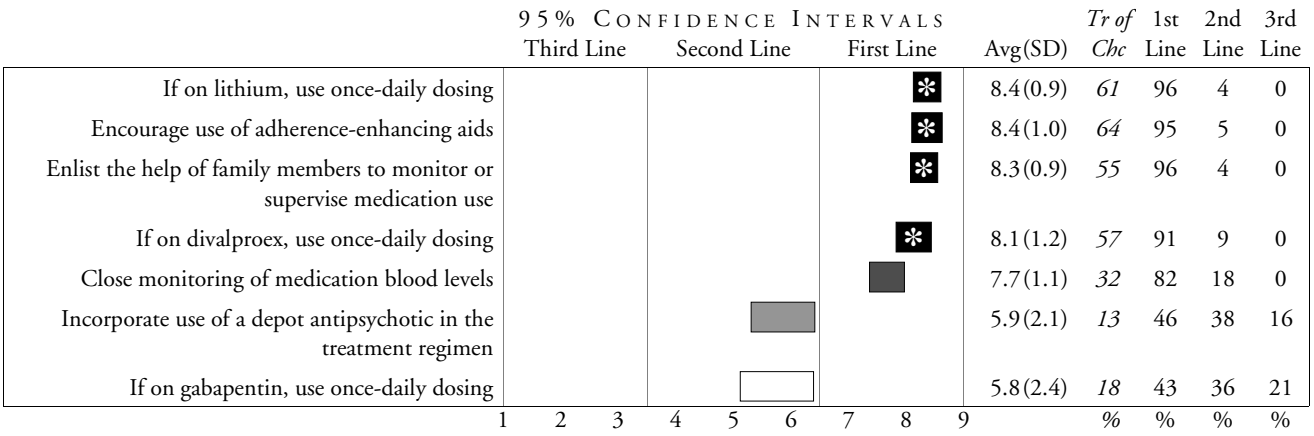


	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Continue present medication, focus on diet and exercise	8.1 (1.1)	*50*	91	9	0
Continue present medication, add topiramate	6.5 (1.8)	*11*	63	25	13
If patient has used only divalproex, attempt gradual switch to lithium	5.8 (1.7)	*7*	31	60	9
Continue present medication but gradually reduce dose	5.5 (2.0)	*7*	35	44	22
If patient has used only lithium, attempt gradual switch to divalproex	5.5 (1.6)	*7*	18	75	7
Attempt gradual switch to carbamazepine	5.4 (1.9)	*5*	32	50	18
Attempt gradual switch to lamotrigine	5.3 (2.0)	*7*	27	52	21
Continue present medication, add nonstimulant appetite suppressant (e.g., sibutramine)	4.8 (1.7)	*0*	18	55	27
Continue present medication, add thyroid hormone	4.7 (1.9)	*0*	16	55	29
Attempt gradual switch to gabapentin	4.3 (1.8)	*2*	18	41	41
Continue present medication, add stimulant (unless contraindicated by history of mood switching on antidepressants)	4.0 (1.8)	*0*	9	45	46
Continue present medication and add a histamine$_2$ blocker	3.9 (1.8)	*0*	7	50	43
		%	%	%	%

42 **Managing weight gain on atypical antipsychotics.** A patient with suboptimal response to the combination of lithium and divalproex improves markedly with the addition of an atypical antipsychotic. Unfortunately, on this regimen the patient gains an average of 4 to 6 pounds per month despite exercise and dieting. Please rate the following interventions to address the weight gain.



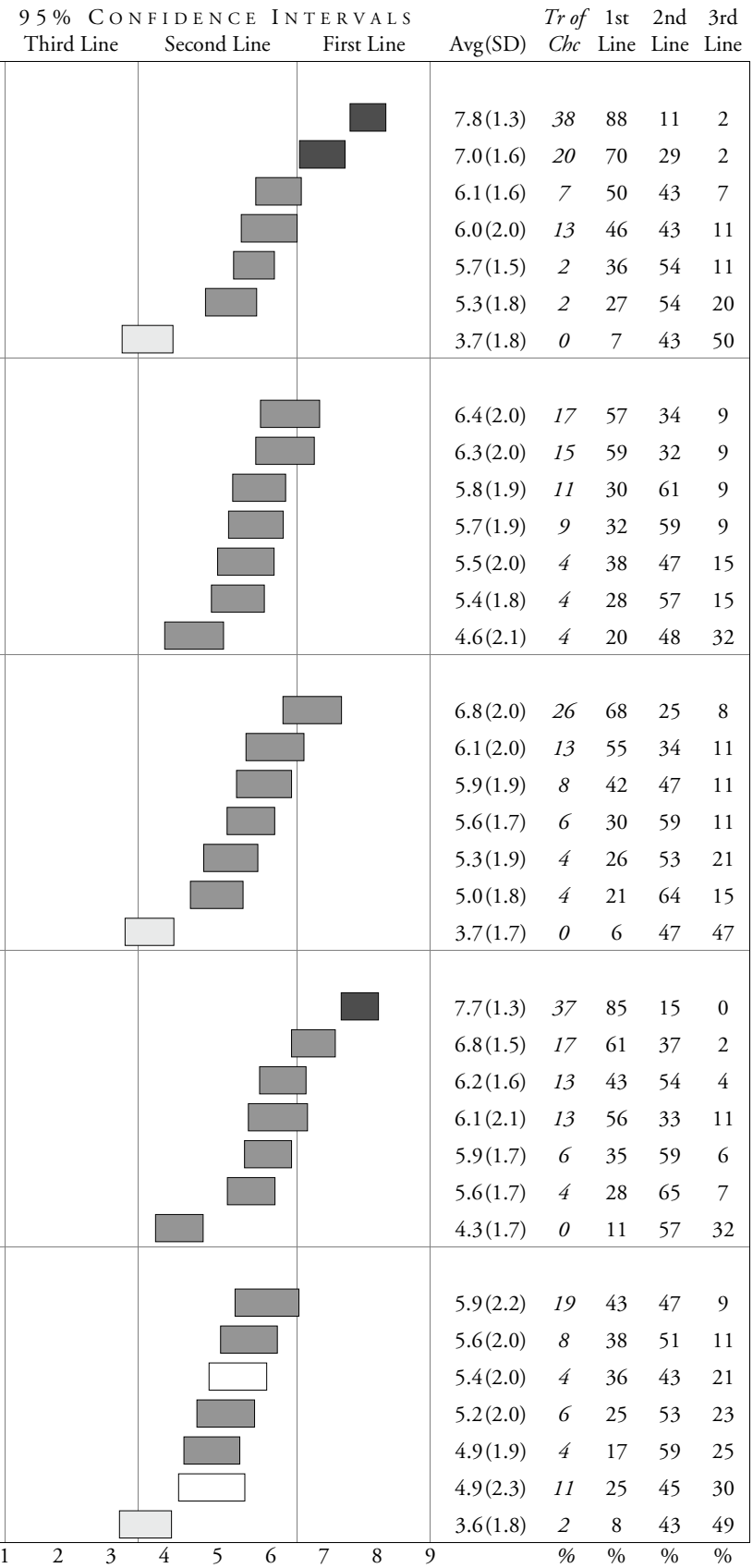
43 **Nonadherence to medication regimen.** Please rate the following strategies for a patient with a history of poor adherence to multiple medication regimens.



44–46 **Management of special problems: selecting medications when one must be used.** Please rate each medication for use in a patient with bipolar disorder who also has the comorbid condition, specific symptom, or demographic profile shown below. Assume the particular patient absolutely must be on a mood stabilizer or antipsychotic. We are not asking you to rate the medications as monotherapy or for specific phases of bipolar disorder, but only as to their general safety or desirability for inclusion in a treatment plan for a bipolar patient with the condition noted.

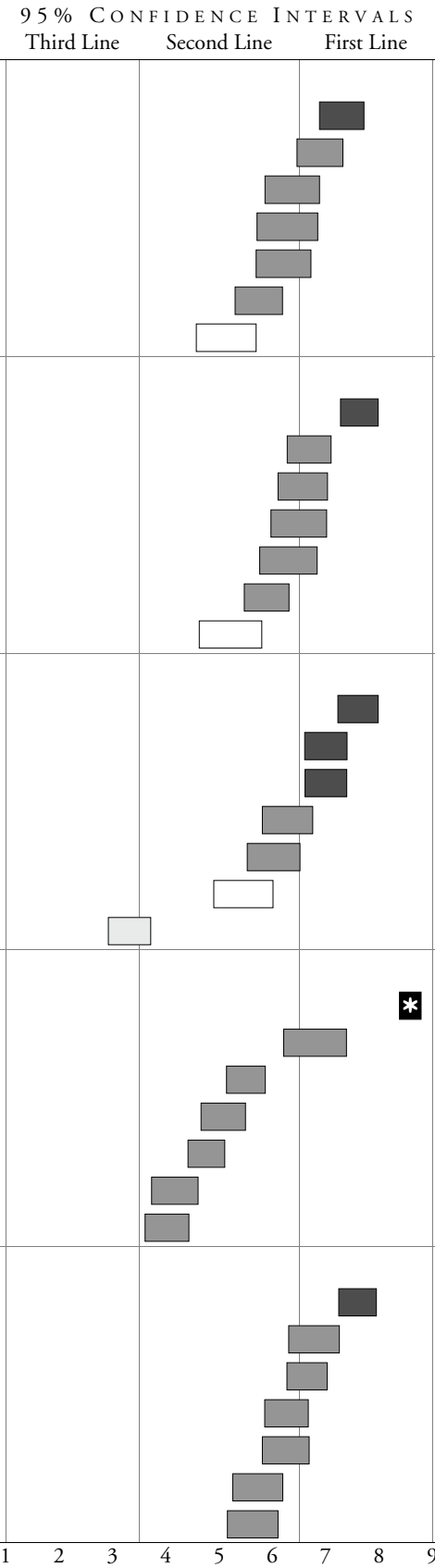
	95% Confidence Intervals Third Line / Second Line / First Line	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Marked Insomnia						
Divalproex		7.8 (1.3)	*36*	83	17	0
Atypical antipsychotic		7.6 (1.4)	*30*	83	15	2
Carbamazepine		6.8 (1.4)	*13*	57	43	0
Gabapentin		6.7 (2.0)	*23*	62	28	9
Lithium		6.4 (1.6)	*13*	49	47	4
Conventional antipsychotic		6.2 (1.9)	*9*	51	36	13
Lamotrigine		5.7 (1.7)	*8*	32	55	13
Marked Psychomotor Agitation						
Divalproex		7.9 (1.4)	*42*	91	8	2
Atypical antipsychotic		7.9 (1.4)	*42*	89	9	2
Carbamazepine		6.9 (1.6)	*17*	62	36	2
Lithium		6.8 (1.6)	*15*	64	30	6
Conventional antipsychotic		6.5 (2.0)	*17*	62	29	10
Gabapentin		6.1 (2.2)	*17*	51	32	17
Lamotrigine		5.4 (1.7)	*8*	23	66	11
Marked Psychomotor Retardation						
Lithium		7.3 (1.4)	*25*	74	26	0
Lamotrigine		6.6 (1.8)	*19*	57	38	6
Divalproex		6.3 (1.8)	*13*	45	45	9
Carbamazepine		6.1 (1.6)	*9*	43	51	6
Atypical antipsychotic		5.9 (2.0)	*9*	43	42	15
Gabapentin		5.4 (1.9)	*6*	28	53	19
Conventional antipsychotic		4.0 (1.9)	*2*	11	45	43
Marked Aggression, Violence						
Divalproex	*	8.3 (1.1)	*57*	93	8	0
Atypical antipsychotic		7.7 (1.2)	*36*	83	17	0
Carbamazepine		7.4 (1.4)	*28*	77	23	0
Lithium		7.4 (1.3)	*27*	77	23	0
Conventional antipsychotic		6.5 (1.8)	*17*	53	42	6
Gabapentin		5.3 (1.9)	*8*	28	51	21
Lamotrigine		5.1 (1.6)	*6*	19	64	17
	1 2 3 4 5 6 7 8 9		*%*	%	%	%

44–46. Management of special problems: selecting medications when one must be used, *continued*



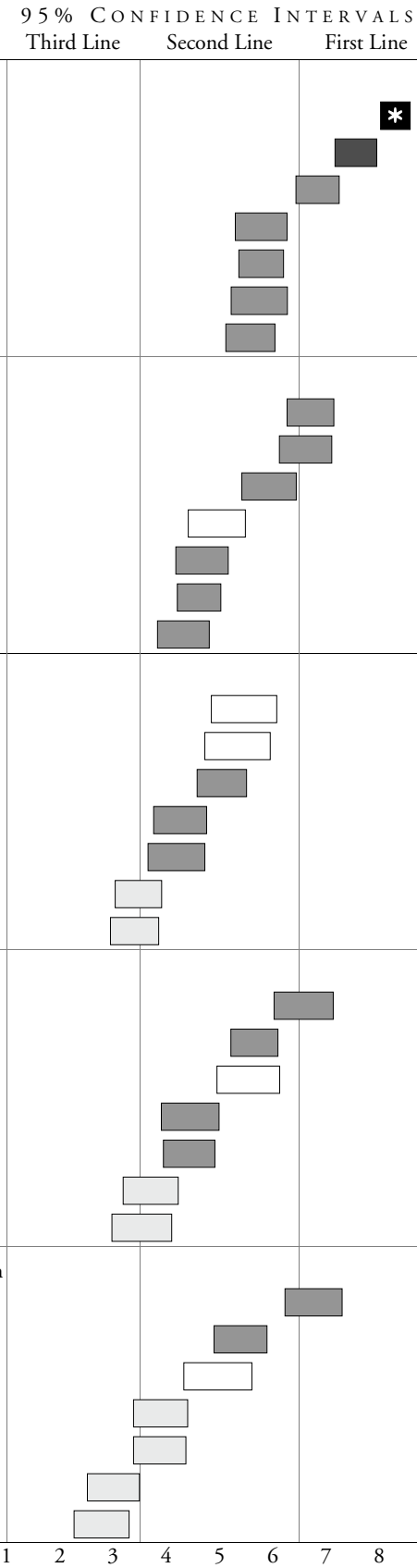
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Panic Disorder					
Divalproex	7.8(1.3)	*38*	88	11	2
Gabapentin	7.0(1.6)	*20*	70	29	2
Carbamazepine	6.1(1.6)	*7*	50	43	7
Lithium	6.0(2.0)	*13*	46	43	11
Lamotrigine	5.7(1.5)	*2*	36	54	11
Atypical antipsychotic	5.3(1.8)	*2*	27	54	20
Conventional antipsychotic	3.7(1.8)	*0*	7	43	50
Obsessive-Compulsive Disorder					
Divalproex	6.4(2.0)	*17*	57	34	9
Lithium	6.3(2.0)	*15*	59	32	9
Atypical antipsychotic	5.8(1.9)	*11*	30	61	9
Gabapentin	5.7(1.9)	*9*	32	59	9
Carbamazepine	5.5(2.0)	*4*	38	47	15
Lamotrigine	5.4(1.8)	*4*	28	57	15
Conventional antipsychotic	4.6(2.1)	*4*	20	48	32
Attention-Deficit/Hyperactivity Disorder					
Divalproex	6.8(2.0)	*26*	68	25	8
Lithium	6.1(2.0)	*13*	55	34	11
Carbamazepine	5.9(1.9)	*8*	42	47	11
Lamotrigine	5.6(1.7)	*6*	30	59	11
Gabapentin	5.3(1.9)	*4*	26	53	21
Atypical antipsychotic	5.0(1.8)	*4*	21	64	15
Conventional antipsychotic	3.7(1.7)	*0*	6	47	47
Posttraumatic Stress Disorder					
Divalproex	7.7(1.3)	*37*	85	15	0
Carbamazepine	6.8(1.5)	*17*	61	37	2
Gabapentin	6.2(1.6)	*13*	43	54	4
Lithium	6.1(2.1)	*13*	56	33	11
Atypical antipsychotic	5.9(1.7)	*6*	35	59	6
Lamotrigine	5.6(1.7)	*4*	28	65	7
Conventional antipsychotic	4.3(1.7)	*0*	11	57	32
Bulimia Nervosa					
Divalproex	5.9(2.2)	*19*	43	47	9
Carbamazepine	5.6(2.0)	*8*	38	51	11
Lamotrigine	5.4(2.0)	*4*	36	43	21
Gabapentin	5.2(2.0)	*6*	25	53	23
Atypical antipsychotic	4.9(1.9)	*4*	17	59	25
Lithium	4.9(2.3)	*11*	25	45	30
Conventional antipsychotic	3.6(1.8)	*2*	8	43	49
		%	%	%	%

44–46. Management of special problems: selecting medications when one must be used, *continued*



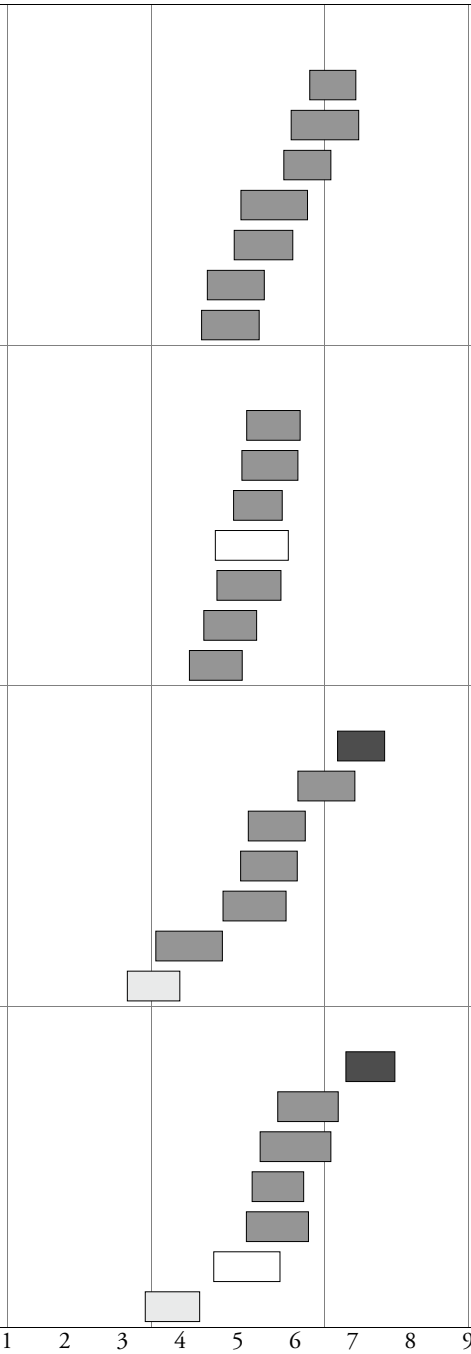
	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Alcohol Abuse					
Divalproex	7.3 (1.5)	*28*	72	28	0
Lithium	6.9 (1.6)	*17*	65	33	2
Atypical antipsychotic	6.4 (1.9)	*15*	50	44	6
Gabapentin	6.3 (2.1)	*17*	52	33	15
Carbamazepine	6.2 (1.9)	*15*	48	46	6
Lamotrigine	5.7 (1.7)	*6*	32	59	9
Conventional antipsychotic	5.1 (2.1)	*8*	30	43	26
Other Substance Abuse					
Divalproex	7.6 (1.3)	*32*	83	17	0
Carbamazepine	6.7 (1.5)	*15*	57	41	2
Lithium	6.6 (1.7)	*11*	60	34	6
Atypical antipsychotic	6.5 (1.9)	*15*	60	32	8
Gabapentin	6.3 (2.0)	*13*	52	37	11
Lamotrigine	5.9 (1.6)	*6*	32	63	6
Conventional antipsychotic	5.2 (2.2)	*6*	33	39	29
Renal Insufficiency					
Divalproex	7.6 (1.4)	*36*	83	17	0
Atypical antipsychotic	7.0 (1.5)	*19*	66	34	0
Carbamazepine	7.0 (1.4)	*19*	66	34	0
Lamotrigine	6.3 (1.7)	*11*	47	43	9
Conventional antipsychotic	6.0 (1.8)	*9*	43	47	9
Gabapentin	5.5 (2.1)	*9*	36	42	23
Lithium	3.3 (1.5)	*0*	2	46	52
Liver Disease					
Lithium	8.6 (0.7)	*70*	96	4	0
Gabapentin	6.8 (2.2)	*28*	69	17	15
Atypical antipsychotic	5.5 (1.3)	*2*	20	76	4
Lamotrigine	5.1 (1.6)	*0*	17	67	17
Conventional antipsychotic	4.8 (1.3)	*0*	7	70	22
Carbamazepine	4.2 (1.6)	*0*	11	54	35
Divalproex	4.0 (1.5)	*0*	6	54	41
Heart Disease					
Divalproex	7.6 (1.3)	*30*	83	17	0
Gabapentin	6.8 (1.8)	*15*	69	24	7
Atypical antipsychotic	6.7 (1.4)	*9*	61	39	0
Lamotrigine	6.3 (1.5)	*9*	44	50	6
Lithium	6.3 (1.6)	*8*	40	55	6
Carbamazepine	5.7 (1.7)	*6*	37	50	13
Conventional antipsychotic	5.6 (1.8)	*6*	35	52	13
		%	%	%	%

44–46. Management of special problems: selecting medications when one must be used, *continued*



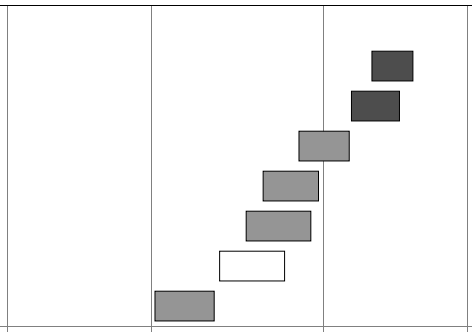
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Stroke or Head Injury Resulting in Mania					
Divalproex	8.3(1.0)	*59*	93	7	0
Carbamazepine	7.6(1.4)	*33*	82	19	0
Atypical antipsychotic	6.8(1.5)	*17*	61	37	2
Gabapentin	5.8(1.8)	*6*	37	48	15
Lithium	5.8(1.6)	*7*	26	67	7
Conventional antipsychotic	5.7(2.0)	*11*	39	44	17
Lamotrigine	5.6(1.7)	*6*	32	57	11
Concern About Weight Gain					
Carbamazepine	6.7(1.6)	*13*	65	28	7
Lamotrigine	6.6(1.8)	*17*	56	35	9
Gabapentin	5.9(1.9)	*6*	43	44	13
Lithium	4.9(2.0)	*2*	28	48	24
Divalproex	4.7(1.8)	*0*	20	54	26
Conventional antipsychotic	4.6(1.5)	*2*	11	61	28
Atypical antipsychotic	4.3(1.8)	*4*	11	52	37
Young Woman Wishing to Become Pregnant					
Conventional antipsychotic	5.5(2.3)	*15*	35	40	26
Lithium	5.3(2.3)	*7*	35	41	24
Atypical antipsychotic	5.0(1.7)	*0*	24	56	20
Gabapentin	4.3(1.9)	*0*	11	46	44
Lamotrigine	4.2(2.0)	*2*	9	52	39
Carbamazepine	3.5(1.6)	*0*	6	40	55
Divalproex	3.4(1.7)	*0*	6	42	53
Trying to Get Pregnant and Needing Medication					
Conventional antipsychotic	6.6(2.1)	*15*	63	22	15
Atypical antipsychotic	5.7(1.7)	*2*	32	57	11
Lithium	5.5(2.2)	*9*	37	41	22
Gabapentin	4.4(2.0)	*2*	17	44	39
Lamotrigine	4.4(1.8)	*2*	9	54	37
Carbamazepine	3.7(1.9)	*0*	9	35	56
Divalproex	3.5(2.1)	*0*	9	28	63
First Trimester of Pregnancy, Needing Medication					
Conventional antipsychotic	6.8(2.0)	*22*	63	26	11
Atypical antipsychotic	5.4(1.8)	*4*	28	54	19
Lithium	5.0(2.4)	*11*	24	46	30
Gabapentin	3.9(1.9)	*0*	9	44	46
Lamotrigine	3.9(1.8)	*0*	4	50	46
Carbamazepine	3.0(1.8)	*0*	7	20	72
Divalproex	2.8(1.9)	*0*	7	15	78
		%	%	%	%

44–46. Management of special problems: selecting medications when one must be used, *continued*



	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
2nd or 3rd Trimester of Pregnancy and Needing Medication					
Lithium	6.7 (1.5)	*11*	56	43	2
Conventional antipsychotic	6.5 (2.2)	*21*	55	30	15
Atypical antipsychotic	6.2 (1.5)	*8*	42	55	4
Divalproex	5.6 (2.1)	*7*	39	43	19
Carbamazepine	5.4 (1.9)	*4*	33	52	15
Gabapentin	5.0 (1.8)	*2*	22	52	26
Lamotrigine	4.9 (1.9)	*2*	20	54	26
Postpartum, Breast-Feeding, and Needing Medication					
Atypical antipsychotic	5.6 (1.7)	*4*	29	62	10
Divalproex	5.6 (1.8)	*6*	23	67	10
Carbamazepine	5.4 (1.5)	*4*	21	71	8
Lithium	5.2 (2.3)	*8*	34	40	26
Conventional antipsychotic	5.2 (2.0)	*8*	23	52	25
Gabapentin	4.9 (1.7)	*2*	17	60	23
Lamotrigine	4.6 (1.7)	*2*	10	67	23
Prepubertal Child					
Lithium	7.1 (1.5)	*24*	73	28	0
Divalproex	6.5 (1.8)	*17*	60	35	6
Carbamazepine	5.7 (1.8)	*8*	35	58	8
Atypical antipsychotic	5.5 (1.8)	*4*	29	64	8
Gabapentin	5.3 (2.0)	*6*	27	56	17
Lamotrigine	4.2 (2.1)	*2*	14	52	35
Conventional antipsychotic	3.5 (1.7)	*2*	4	42	54
Adolescent Girl					
Lithium	7.3 (1.5)	*28*	76	22	2
Carbamazepine	6.2 (1.9)	*12*	51	43	6
Divalproex	6.0 (2.2)	*15*	50	37	14
Atypical antipsychotic	5.7 (1.6)	*4*	31	65	4
Gabapentin	5.7 (2.0)	*8*	35	49	16
Lamotrigine	5.2 (2.1)	*4*	31	45	24
Conventional antipsychotic	3.9 (1.7)	*2*	8	45	47
		%	%	%	%

44–46. Management of special problems: selecting medications when one must be used, *continued*

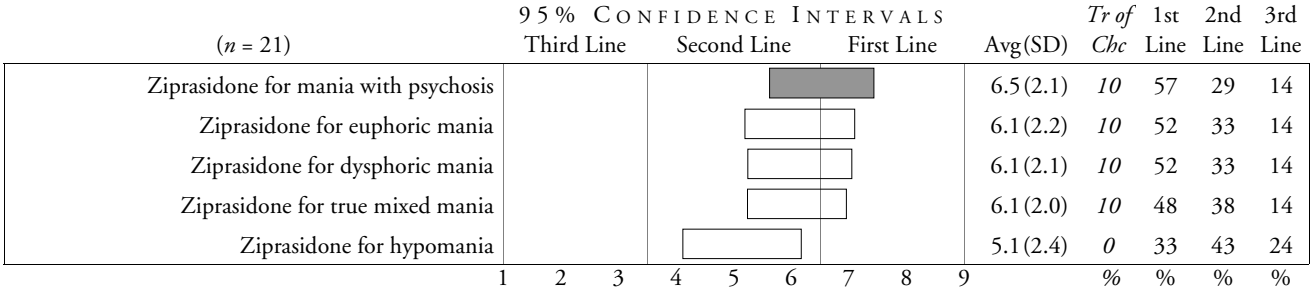


	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Adolescent Boy					
Divalproex	7.7(1.3)	*37*	86	14	0
Lithium	7.4(1.5)	*29*	77	22	2
Carbamazepine	6.5(1.6)	*14*	54	42	4
Atypical antipsychotic	5.9(1.8)	*6*	39	56	6
Gabapentin	5.7(2.0)	*10*	37	47	16
Lamotrigine	5.3(2.1)	*4*	29	48	23
Conventional antipsychotic	4.1(1.9)	*4*	12	44	44
Elderly Patient With Dementia					
Divalproex	7.6(1.2)	*32*	85	15	0
Atypical antipsychotic	7.2(1.6)	*30*	67	33	0
Carbamazepine	6.1(1.8)	*13*	44	44	11
Gabapentin	5.7(2.1)	*9*	37	43	20
Conventional antipsychotic	5.4(2.1)	*7*	35	40	26
Lithium	5.3(1.6)	*2*	20	67	13
Lamotrigine	5.2(1.7)	*4*	17	67	17
		%	%	%	%

Drug in Development: Ziprasidone

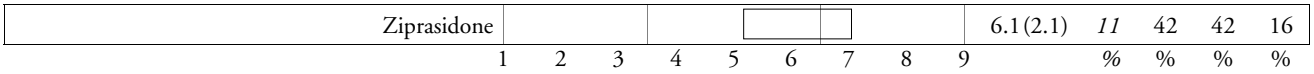
Because ziprasidone is not yet approved for use in the United States, in questions 3, 10, and 18, we instructed the experts to rate it only if they had used it in a clinical trial or had other first-hand experience. Twenty-one experts had had some experience with ziprasidone. On this page, we present the ratings for ziprasidone from the 4 questions in which it was included as an option and indicate the number of experts (*n*) who rated it. Readers should keep in mind that in each of the questions below, ziprasidone was rated in comparison with the currently available antipsychotics.

3 **Treatment of mania: first episode, choice of antipsychotic.** In the situation described in question 1, assume you have decided to use an oral antipsychotic as part of your initial treatment plan. Please rate each of the following as an initial choice in each of the symptom presentations.



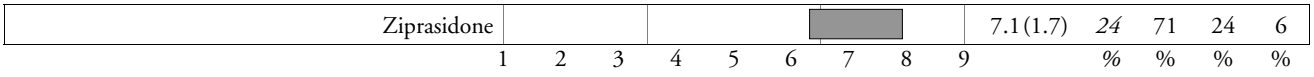
(*n* = 21)	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Ziprasidone for mania with psychosis	6.5 (2.1)	*10*	57	29	14
Ziprasidone for euphoric mania	6.1 (2.2)	*10*	52	33	14
Ziprasidone for dysphoric mania	6.1 (2.1)	*10*	52	33	14
Ziprasidone for true mixed mania	6.1 (2.0)	*10*	48	38	14
Ziprasidone for hypomania	5.1 (2.4)	*0*	33	43	24
		%	%	%	%

10 **Choice of agents for long-term antipsychotic maintenance.** Suppose you have determined that a patient needs long-term maintenance with an oral antipsychotic along with a mood stabilizer. Regardless of your recommendation for choice of antipsychotics during the acute phase, please rate each of the following for long-term use in this situation.



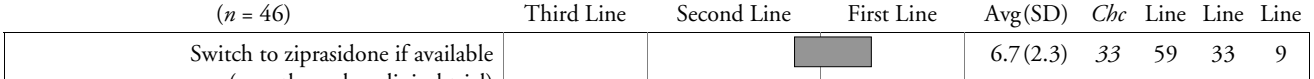
(*n* = 19)	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Ziprasidone	6.1 (2.1)	*11*	42	42	16
		%	%	%	%

18 **Bipolar depression with psychosis: choice of antipsychotic.** Assume you have decided to use an antipsychotic in the acute-phase treatment of a patient with bipolar depression with psychotic features. Please rate the following options.



(*n* = 17)	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Ziprasidone	7.1 (1.7)	*24*	71	24	6
		%	%	%	%

42 **Managing weight gain on atypical antipsychotics.** A patient with suboptimal response to the combination of lithium and divalproex improves markedly with the addition of an atypical antipsychotic. Unfortunately, on this regimen the patient gains an average of 4 to 6 pounds per month despite exercise and dieting. Please rate the following interventions to address the weight gain.



(*n* = 46)	Avg (SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Switch to ziprasidone if available (e.g., through a clinical trial)	6.7 (2.3)	*33*	59	33	9
		%	%	%	%

Treatment of Bipolar Disorder: A Guide for Patients and Families

David A. Kahn, M.D., Ruth Ross, M.A., David J. Printz, M.D., and Gary S. Sachs, M.D.

Bipolar disorder (also known as manic-depressive illness) is a severe biological disorder that affects approximately 1.2% of the adult population (more than 2.2 million people in the United States). Although the symptoms and severity vary, bipolar disorder almost always has a powerful impact on those who have the illness as well as on their family members, partners, and friends. If you or someone you care about has been diagnosed with bipolar disorder, you may have many questions about the nature of the illness, its causes, and the treatments that are available. This guide is intended to answer some of the most commonly asked questions about bipolar disorder.

WHAT IS BIPOLAR DISORDER?

As human beings, we all experience a variety of moods—happiness, sadness, anger, to name a few. Unpleasant moods and changes in mood are normal reactions in everyday life, and we can often identify the events that caused our mood to change. However, when we experience changes in mood—or extremes of mood—that are out of proportion to events or come "out of the blue" and make it hard for us to function, these changes are often the result of a *mood disorder*.

Mood disorders are biological illnesses that affect our ability to experience normal mood states. There are 2 general groups of mood disorders: *unipolar depressive disorders*, in which all abnormal mood changes involve a lowering of mood, and *bipolar disorders*, in which at least some of the mood changes involve abnormal elevation of mood. All mood disorders are caused by changes in brain chemistry. They are not the fault of the person suffering from them. They are not the result of a "weak" or unstable personality. Rather, mood disorders are treatable medical illnesses for which there are specific medications that help most people.

How is the diagnosis made?

Although bipolar disorder is clearly a biological disease, there are no laboratory tests or other procedures that a doctor can use to make a definitive diagnosis. Instead, the doctor diagnoses the illness based on a group of symptoms that occur together. To make an accurate diagnosis, the doctor will need to take a careful history of the symptoms the person is currently experiencing as well as any symptoms he or she has had in the past.

What are the symptoms of bipolar disorder?

Bipolar disorder is a disease in which the person's mood changes in *cycles* over time. Over the course of the illness, the person experiences periods of elevated mood, periods of depressed mood, and times when mood is normal. There are 4 different kinds of mood episodes that occur in bipolar disorder:

Mania (manic episode). Mania often begins with a pleasurable sense of heightened energy, creativity, and social ease. However, these feelings quickly progress to full-blown euphoria (extremely elevated mood) or severe irritability. People with mania typically lack insight, deny that anything is wrong, and angrily blame anyone who points out a problem. In a manic episode, the following symptoms are present for at least 1 week and make it very difficult for the person to function:

- Feeling unusually "high," euphoric, or irritable

Plus at least 4 of the following symptoms:

- Needing little sleep yet having great amounts of energy
- Talking so fast that others cannot follow you
- Having racing thoughts
- Being so easily distracted that your attention shifts between many topics in just a few minutes
- Having an inflated feeling of power, greatness, or importance
- Doing reckless things without concern about possible bad consequences (e.g., spending too much money, inappropriate sexual activity, or making foolish business investments)

In severe cases, the person may also experience psychotic symptoms such as hallucinations (hearing or seeing things that are not there) or delusions (firmly believing things that are not true).

Hypomania (hypomanic episode). Hypomania is a milder form of mania that has similar but less severe symptoms and causes less impairment. During a hypomanic episode, the person may have an elevated mood, feel better than usual, and be more productive. These episodes often feel good and the quest for hypomania may even cause some individuals with bipolar disorder to stop their medication. However, hypomania can rarely be maintained indefinitely, and is often followed by an escalation to mania or a crash to depression.

Depression (major depressive episode). In a major depressive episode, the following symptoms are present for at least 2 weeks and make it difficult for the person to function:

- Feeling sad, blue, or down in the dumps or losing interest in the things one normally enjoys

Plus at least 4 of the following symptoms:

- Difficulty sleeping or sleeping too much
- Loss of appetite or eating too much
- Problems concentrating or making decisions
- Feeling slowed down or feeling too agitated to sit still
- Feeling worthless or guilty or having very low self-esteem
- Thoughts of suicide or death

Severe depressions may also include hallucinations or delusions.

Mixed Episode. Perhaps the most disabling episodes are those that involve symptoms of both mania and depression occurring at the same time or alternating frequently during the day. Individuals are excitable or agitated as in mania but also feel irritable and depressed. Owing to the combination of high energy and depression, mixed episodes present the greatest risk of suicide.

What are the different patterns of bipolar disorder?

People with bipolar disorder vary in the types of episodes they usually have and how often they become ill. Some individuals have equal numbers of manic and depressive episodes; others have mostly one type or the other. The average person with bipolar disorder has 4 episodes during the first 10 years of the illness. Men are more likely to start with a manic episode, women with a depressive episode. While a number of years can elapse between the first 2 or 3 episodes

of mania or depression, without treatment most people eventually have more frequent episodes. Sometimes these follow a seasonal pattern (for example, becoming hypomanic in the summer and depressed in the winter). A small number of people cycle frequently or even continuously throughout the year (termed "rapid-cycling" bipolar disorder).

Episodes can last days, months, or sometimes even years. On average, without treatment, manic or hypomanic episodes last a few months, while depressions often last well over 6 months. Some individuals recover completely between episodes and may go many years without any symptoms, while others continue to have low-grade but troubling depression or mild swings up and down.

Special terms are used to describe these common patterns:

- In **Bipolar I Disorder**, a person has manic or mixed episodes and almost always has depressions as well. If someone becomes ill for the first time with a manic episode, the illness is still considered bipolar even though depressions have not yet occurred. It is highly likely that future episodes will involve depression as well as mania unless effective treatment is received.

- In **Bipolar II Disorder**, a person has only hypomanic and depressive episodes, not full manic or mixed episodes. This type is often hard to recognize because hypomania may seem normal if the person is very productive and avoids getting into serious trouble. Individuals with bipolar II disorder frequently overlook episodes of hypomania and seek treatment only for depression. Unfortunately, if a mood stabilizer is not prescribed with an antidepressant for unrecognized bipolar II disorder, the antidepressant may trigger a "high" or set off more frequent cycles.

- In **Rapid-Cycling Bipolar Disorder**, a person has at least 4 episodes per year, in any combination of manic, hypomanic, mixed, or depressive episodes. This course pattern is seen in approximately 5% to 15% of patients with bipolar disorder. It is sometimes associated with use of antidepressants without mood stabilizers, which may increase cycling. For unknown reasons, the rapid-cycling subtype of bipolar disorder is more common in women.

Are there other psychiatric conditions that may be confused with, or coexist with, bipolar disorder?

Bipolar disorder can be confused with other disorders, including a variety of anxiety disorders and psychotic disorders (such as schizophrenia and schizoaffective disorder). This is because anxiety and psychotic symptoms often occur during the course of bipolar disorder. Individuals with bipolar disorder also frequently suffer from psychiatric disorders that are "comorbid" with (are present in addition to) the bipolar illness. The most common of these comorbid conditions are substance abuse disorders, obsessive-compulsive disorder, and panic disorder. If you have any concerns about whether your diagnosis is correct, you should feel comfortable asking the doctor to explain how he or she arrived at a diagnosis of bipolar disorder.

When does bipolar disorder begin?

Bipolar disorder usually begins in adolescence or early adulthood, although it can sometimes start in early childhood or as late as the 40s or 50s. When someone over 50 has a manic episode for the first time, the cause is more likely to be a problem imitating bipolar disorder, such as a neurological illness or the effects of drugs, alcohol, or some prescription medications.

Why is it important to diagnose and treat bipolar disorder as early as possible?

On average, people with bipolar disorder see 3 to 4 doctors and spend over 8 years seeking treatment before they receive a correct diagnosis. Earlier diagnosis, proper treatment, and finding the right medications can help people avoid the following:

- ***Suicide.*** The risk is highest in the initial years of the illness. Over the course of the illness nearly 1 out of 5 individuals with bipolar disorder will die from suicide, making it one of the most lethal psychiatric illnesses.
- ***Alcohol/substance abuse.*** More than 50% of those with bipolar disorder abuse alcohol or drugs during their illness. While some individuals may use substances in an attempt to "self-medicate" symptoms of bipolar illness, individuals with a combination of substance abuse and bipolar illness have a worse outcome.
- ***Marital and work problems.*** Prompt treatment improves the prospects for a stable marriage and productive work.
- ***Treatment difficulties.*** In some individuals, it appears that episodes become more frequent and harder to treat over time. This is sometimes referred to as "kindling."
- ***Incorrect, inappropriate, or partial treatment.*** A person misdiagnosed as having depression alone instead of bipolar disorder may incorrectly receive antidepressants alone without a mood stabilizing medication. This can trigger manic episodes and make the overall course of the illness worse.

What causes bipolar disorder?

There is no single, proven cause of bipolar disorder, but research suggests that it is the result of abnormalities in the way some nerve cells in the brain function or communicate. Whatever the precise nature of the biochemical problem underlying bipolar illness, it clearly makes people with the disorder more vulnerable to emotional and physical stresses. As a result, upsetting life experiences, substance use, lack of sleep, or other stresses can trigger episodes of illness, even though these stresses do not actually cause the disorder.

This theory of an inborn vulnerability interacting with an environmental trigger is similar to theories proposed for many other medical conditions. In heart disease, for example, a person might inherit a tendency to have high cholesterol or high blood pressure, which can cause gradual damage to the heart's supply of oxygen. During stress, such as physical exertion or emotional tension, the person might suddenly develop chest pain or have a heart attack if the oxygen supply becomes too low. The treatment in this case is to take medication to lower the cholesterol or blood pressure (treating the underlying illness) and make changes in lifestyle (e.g., exercise, diet, reducing stresses that can trigger acute episodes). Similarly, in bipolar disorder, we use mood stabilizers to treat the underlying biological disorder while at the same time recommending changes in lifestyle (e.g., reducing stress, good sleep habits, avoiding substances of abuse) to lower the risk of relapse.

Is bipolar disorder inherited?

Bipolar disorder tends to run in families. Researchers have identified a number of genes that may be linked to the disorder, suggesting that several different biochemical problems may occur in bipolar disorder. Like other complex inherited disorders, bipolar disorder only occurs in a fraction of the individuals at genetic risk. For

example, if an individual has bipolar disorder and his or her spouse does not, there is only a 1 in 7 chance that their child will develop it. The chance may be greater if you have a greater number of relatives with bipolar disorder or depression.

HOW IS BIPOLAR DISORDER TREATED?

Stages of Treatment

- ***Acute phase:*** treatment is aimed at ending the current manic, hypomanic, depressive, or mixed episode
- ***Preventive or maintenance phase:*** treatment is continued on a long-term basis to prevent future episodes

Components of Treatment

- ***Medication*** is necessary for nearly all patients during acute and preventive phases.
- ***Education*** is crucial in helping patients and families learn how best to manage bipolar disorder and prevent its complications.
- ***Psychotherapy*** helps patients and families affected by bipolar disorder deal with disturbing thoughts, feelings, and behaviors in a constructive manner.

TYPES OF MEDICATION

The 3 most important types of medication used to control the symptoms of bipolar disorder are ***mood stabilizers***, ***antidepressants***, and ***antipsychotics***. Your doctor may also prescribe other medications to help with insomnia, anxiety, or restlessness. While we do not understand how some of these medications work, we do know that all of them affect chemicals in the brain called neurotransmitters, which are involved in the functioning of nerve cells.

What are mood stabilizers?

Medications are considered mood stabilizers if they have 2 properties: 1) they provide relief from acute episodes of mania or depression, or prevent them from occurring; and 2) they do not worsen depression or mania or lead to increased cycling.

Lithium, divalproex and carbamazepine have been shown to meet this definition; the first 2 are the best established and most widely used. Divalproex and carbamazepine were originally developed as anticonvulsants for the control of epilepsy, another brain disorder. Other available medications that are undergoing research as promising mood stabilizers include several new anticonvulsants and the newer "atypical" antipsychotics. Electroconvulsive therapy (ECT), discussed later, is also considered a mood stabilizing treatment.

Lithium (brand names Eskalith, Lithobid, Lithonate)

The first known mood stabilizer, lithium, is actually an element rather than a compound (a substance synthesized by a laboratory). Lithium was first found to have behavioral effects in the 1950s and has been used as a mood stabilizer in the United States for 30 years. Lithium appears to be most effective for individuals with more "pure" or euphoric mania (where there is little depression mixed in with the elevated mood). It is also helpful for depression, especially when added to other medications. Lithium appears to be less effective in mixed manic episodes and in rapid-cycling bipolar disorder. Monitoring blood levels of lithium can reduce side effects and ensure that the patient is receiving an adequate dose to help produce the best response. Common side effects of lithium include weight gain, tremor, nausea, and increased urination. Lithium may affect the thyroid gland and the kidneys, so that periodic blood tests are needed to be sure they are functioning properly.

Divalproex (brand name Depakote)

Divalproex has been used as an anticonvulsant—to treat seizures—for several decades. It has also been extensively researched as a mood stabilizer in bipolar illness. Divalproex is equally effective in both euphoric and mixed manic episodes. It is also effective in rapid cycling bipolar disorder and for individuals whose illness is complicated by substance abuse or anxiety disorders. Unlike other mood stabilizers, divalproex can be given in relatively large initial doses for acute mania, which may produce a more rapid response. Common side effects of divalproex include sedation, weight gain, tremor, and gastrointestinal problems. Blood level monitoring and dose adjustments may help minimize side effects. Divalproex may cause a mild liver inflammation and may affect the production of a type of blood cell called platelets. Although it is quite rare for there to be any serious complications from these potential effects, it is important to monitor liver function tests and platelet counts periodically.

Other anticonvulsants used as mood stabilizers

- ***Carbamazepine*** (Tegretol, Carbatrol). Although fewer clinical studies support the use of carbamazepine, it appears to have a profile similar to divalproex. It, too, has been available for many years, and is effective in a broad range of subtypes of bipolar illness and in both euphoric and mixed manic episodes. Carbamazepine commonly causes sedation and gastrointestinal side effects. Because of a rare risk of bone marrow suppression and liver inflammation, periodic blood testing is also needed during carbamazepine treatment, just as during treatment with divalproex. Because carbamazepine has complicated interactions with many other medications, careful monitoring is needed when it is combined with other medications.
- ***Lamotrigine*** (Lamictal). Lamotrigine is a relatively new medication. Recent research suggests that it can act as a mood stabilizer, and may be especially useful for the depressed phase of bipolar disorder. One serious risk of lamotrigine use is that 3 out of every 1,000 individuals (0.3%) taking the medication develop a serious rash. The risk of rash can be lowered by increasing the dosage very slowly. Aside from the risk of rash, lamotrigine tends to have fewer troublesome side effects overall, but can cause dizziness, headaches, and difficulties with vision.
- ***Gabapentin*** (Neurontin). Gabapentin has become popular as a mood stabilizer, although there has been relatively little research on its use in bipolar disorder. It appears especially helpful in reducing anxiety. One strength of gabapentin is that it is unlikely to interact with other medications, so that it can be easily added to other mood stabilizers to augment their effect. Side effects of gabapentin can include fatigue, sedation, and dizziness.
- ***Topiramate*** (Topomax). Preliminary research suggests that this new anticonvulsant may be helpful in mania. One side effect of topiramate may actually be an advantage. Unlike many of the other mood stabilizers, topiramate does not appear to cause weight gain and may actually help people lose weight. Other side effects may include sedation, dizziness, and cognitive slowing or memory difficulties. It should avoided by people who have had kidney stones.

What are antidepressants?

Antidepressants treat the symptoms of depression. In bipolar disorder, antidepressants must be used together with a mood stabiliz-

ing medication. If used without a mood stabilizer, an antidepressant can push a person with bipolar disorder into a manic state. Many types of antidepressants are available with different chemical mechanisms of action and side effect profiles. Most research with antidepressants has been done in people with unipolar depression—people who have never had a manic episode. In unipolar depression, the available medications are about equally effective. There has been little research on the use of antidepressants in bipolar disorder, but most experts consider the following 3 types to be first choices:

- ***Bupropion*** (Wellbutrin)
- ***Selective serotonin reuptake inhibitors***: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft)
- ***Venlafaxine*** (Effexor).

If these do not work, or if they cause unpleasant side effects, the other choices are:

- Mirtazapine (Remeron)
- Nefazodone (Serzone)
- Monoamine oxidase inhibitors: phenelzine (Nardil), tranylcypromine (Parnate). These are very effective but also require you to stay on a special diet to avoid dangerous side effects.
- Tricyclic antidepressants: amitriptyline (Elavil), desipramine (Norpramin, Pertofrane), imipramine (Tofranil), nortriptyline (Pamelor). Tricyclics may be more likely to cause side effects or to set off manic episodes or rapid cycling.

What are antipsychotic medications?

Antipsychotic medications are used to control psychotic symptoms, such as hallucinations or delusions, that sometimes occur in very severe depressive or manic episodes.

Antipsychotics can be used in 2 additional ways in bipolar disorder, even if no psychotic symptoms are present. They may be used as sedatives, especially during early stages of treatment, for insomnia, anxiety, and agitation. Researchers also believe that the newer antipsychotic medications have mood stabilizing properties, and may help control depression and mania. Antipsychotic medications are therefore often added to mood stabilizers to improve the response in patients who have never had psychotic symptoms. Antipsychotics may also be used alone as mood stabilizers when patients cannot tolerate or do not respond to any of the mood stabilizers.

There are 2 kinds of antipsychotics: older antispychotics (often called "typical" or conventional antipsychotics) and newer antipsychotics (often called atypical antipsychotics). One serious problem with the older antipsychotics is the risk of a permanent movement disorder called tardive dyskinesia (TD). Older antipsychotic medicines may also cause muscle stiffness, restlessness, and tremors. The newer "atypical" antipsychotics have a much lower risk of causing TD (roughly 1% per year) and movement and muscle side effects. Because of this, the newer atypical antipsychotics are usually the first choice in any of the situations when an antipsychotic is needed.

Four atypical antipsychotics, are currently available:

- olanzapine (Zyprexa)
- quetiapine (Seroquel)
- risperidone (Risperdal)
- clozapine (Clozaril)

As mentioned earlier, research is beginning to show that these atypical antipsychotics have mood stabilizing properties. Common side effects of the atypical antipsychotics include drowsiness and weight gain. Although it is very effective, clozapine is not a first choice medication because it can cause a rare and serious blood side effect, requiring weekly or biweekly blood tests.

Examples of conventional antipsychotics include older medications such as haloperidol (Haldol), perphenazine (Trilafon), and chlorpromazine (Thorazine). Although they are not usually a first choice, the older medications can be helpful for patients who do not respond to or have troublesome side effects with the newer atypical antipsychotics.

ACUTE PHASE OF TREATMENT

Selecting a mood stabilizer for an acute manic episode

The first-line drugs for treating a manic episode during the acute phase are lithium and valproate. In choosing between these 2 medications, your doctor will consider your treatment history (whether either of these medicines has worked well for you in the past), the subtype of bipolar disorder you have (e.g., whether you have rapid-cycling bipolar disorder), your current mood state (euphoric or mixed mania), and the particular side effects that you are most concerned about.

Lithium and divalproex are each good choices for "pure" mania (euphoric mood without symptoms of depression), while divalproex is preferred for mixed episodes or for patients who have rapid-cycling bipolar disorder. It is not unusual to combine lithium and divalproex to obtain the best possible response. If this combination is still not fully effective, a third mood stabilizer is sometimes added.

Carbamazepine is a good alternative medication after lithium and divalproex. Like divalproex, carbamazepine may be particularly effective in mixed episodes and in the rapid-cycling subtype. It can be easily combined with lithium, although it is more complicated to combine it with divalproex.

The newer anticonvulsants (lamotrigine, gabapentin, and topiramate) are often best reserved as back-up medications to add to first-line medications for mania, or to use instead of the first-line group if there have been difficult side effects.

How quickly do mood stabilizers work?

It can take a few weeks for a good response to occur with mood stabilizers. However, it is often helpful to combine mood stabilizers with other medications that provide immediate, short-term relief from the insomnia, anxiety, and agitation that often occur during a manic episode. The choices for so-called "adjunctive" medication include:

- antipsychotic medicines, especially if the person is also having psychotic symptoms (see above).
- a sedative called a *benzodiazepine*. Benzodiazpeines include lorazepam (Ativan), clonazepam (Klonopin), and others. They should be carefully supervised, or avoided, in patients who have a history of drug addiction or alcoholism.

Although both benzodiazepine sedatives and antipsychotic medicines can cause drowsiness, the dosages of these medications can generally be lowered as the person recovers from the acute episode. However, some individuals need to continue taking a sedative for a longer period to control certain symptoms such as insomnia or anxiety. Longer-term treatment with an antipsychotic is sometimes needed to prevent relapse.

Selecting an antidepressant for an acute depression

Although a mood stabilizer alone may treat milder depression, an antidepressant is usually needed for more severe depression. It is dangerous to give antidepressants alone in bipolar disorder, because they can trigger an increase in cycling or cause the person's mood to

"overshoot" and switch from depression to hypomania or mania. For this reason, antidepressants are always given in combination with a mood stabilizer in bipolar disorder.

Antidepressants usually take several weeks to show effects. Although the first antidepressant tried will work for the majority of patients, it is common for patients to go through 2 or 3 trials of antidepressants before finding one that is fully effective and doesn't cause troublesome side effects. While waiting for the antidepressant to work, it may be helpful to take a sedating medication to help relieve insomnia, anxiety, or agitation.

If depression persists despite use of an antidepressant with a mood stabilizer, adding lithium (if not already in use) or changing the mood stabilizer might help. Lamotrigine, in particular, may be helpful in depression.

Strategies to limit side effects

All of the medications that are used to treat bipolar disorder can produce bothersome side effects; there are also some serious but rare medical reactions. Just as different people have varying responses to different medications, the type of side effects different people develop can vary widely, and some people may not have any side effects at all. Also, if someone has problems with side effects on 1 medication, this does not mean that that person will develop troublesome side effects on another medication.

Certain strategies can help prevent or minimize side effects. For example, the doctor may want to start at a low dose and adjust the medication to higher doses very slowly. Although this may mean that you need to wait longer to see if the medication will help the symptoms, it does reduce the chances of side effects developing. In the case of lithium or divalproex, blood level monitoring is very important to insure that a patient is receiving enough medication to help, but not more than is necessary. If side effects do occur, the dosage can frequently be adjusted to eliminate the side effects or another medication can be added to help. It is important to discuss your concerns about side effects and any problems you may be experiencing with your doctor, so that he or she can take these into account in planning your treatment.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is often life-saving in severe depression and mania, but has received a lot of undeserved negative publicity. ECT is a critically important option if someone is very suicidal, if the person is severely ill and cannot wait for medications to work (e.g., the person is not eating or drinking), if there is a history of many unsuccessful medication trials, if medical conditions or pregnancy make medications unsafe, or if psychosis (delusions or hallucinations) is present. ECT is administered under anesthesia in a carefully monitored medical setting. Patients typically receive 6 to 10 treatments over a few weeks. The most common side effect of ECT is temporary memory problems, but memory returns quickly after a course of treatment.

About hospitalization

Many patients with bipolar I disorder (i.e., patients who have had at least 1 full manic episode) are hospitalized at some point in the course of their illness. Because acute mania affects insight and judgment, individuals with mania are often hospitalized over their objections, which can be upsetting for both patients and their loved ones. However, most individuals with mania are grateful for the help they received during the acute episode, even if it was given against their will at the time. Hospitalization should be considered under the following circumstances:

- When safety is in question due to suicidal, homicidal, or aggressive impulses or actions
- When severe distress or dysfunction requires round-the-clock care and support (which is difficult, if not impossible, for any family to sustain for a long period of time)
- Where there is ongoing substance abuse, to prevent access to drugs
- When the patient has an unstable medical condition
- When close observation of the patient's reaction to medications is required

PREVENTIVE TREATMENT

Mood stabilizers, especially lithium and divalproex, are the cornerstones of prevention or long-term maintenance treatment. About 1 in 3 people with bipolar disorder will remain completely free of symptoms just by taking mood stabilizing medication for life. Most other people experience a great reduction in the frequency and severity of episodes during maintenance treatment.

It is important not to become overly discouraged when episodes do occur and to recognize that the success of treatment can only be evaluated over the long term, by looking at the frequency and severity of episodes. Be sure to report changes in mood to your doctor immediately, because adjustments in your medicine at the first warning signs can often restore normal mood and head off a full-blown episode. Medication adjustments should be viewed as a routine part of treatment (just as insulin doses are changed from time to time in diabetes). Most patients with bipolar disorder do best on a combination or "cocktail" of medications. Often the best response is achieved with 1 or more mood stabilizers, supplemented from time to time with an antidepressant or possibly an antipsychotic medication.

Continuing to take medication correctly and as prescribed (which is called adherence) on a long-term basis is difficult whether you are being treated for a medical condition (such as high blood pressure or diabetes) or for bipolar disorder. Individuals with bipolar disorder are often tempted to stop taking their medication during maintenance treatment for several reasons. They may feel free of symptoms and think they don't need medication any more. They may find the side effects too hard to deal with. Or they may miss the mild euphoria they experience during hypomanic episodes. However, research clearly indicates that stopping maintenance medication almost always results in relapse, usually in weeks to months after stopping. In the case of lithium discontinuation, the rate of suicide rises precipitously after discontinuation. There is some evidence that stopping lithium in an abrupt fashion (rather than slowly tapering off) carries a much greater risk of relapse. Therefore, if you must discontinue medication, it should be done gradually under the close medical supervision of your doctor.

If someone has had only a single episode of mania, consideration may be given to tapering the medication after about a year. However, if the single episode occurs in someone with a strong family history of bipolar disorder or is particularly severe, longer-term maintenance treatment should be considered. If someone has had 2 or more manic or depressive episodes, experts strongly recommend taking preventive medication indefinitely. The only times to consider stopping a preventive medication that is working well is if a medical condition or severe side effect prevents its safe use, or when a woman is trying to become pregnant. Even these situations

may not be absolute reasons to stop, and substitute medications can often be found. You should discuss each of these situations carefully with your doctor.

EDUCATION: LEARNING TO COPE WITH BIPOLAR DISORDER

Another important part of treatment is education. The more you and your family and loved ones learn about bipolar disorder and its treatment, the better you will be able to cope with it.

Is there anything I can do to help my treatment?

Absolutely, yes. First, you should become an expert on your illness. Since bipolar disorder is a lifetime condition, it is essential that you and your family or others close to you learn all about it and its treatment. Read books, attend lectures, talk to your doctor or therapist, and consider joining a chapter of the National Depressive and Manic-Depressive Association (NDMDA) or the National Alliance for the Mentally Ill (NAMI) near you to stay up to date on medical and other developments, as well as to learn from others about managing the illness. Being an informed patient is the surest path to success.

You can often help reduce the minor mood swings and stresses that sometimes lead to more severe episodes by paying attention to the following:

- **Maintain a stable sleep pattern.** Go to bed around the same time each night and get up about the same time each morning. Disrupted sleep patterns appear to cause chemical changes in your body that can trigger mood episodes. If you have to take a trip where you will change time zones and might have jet lag, get advice from your doctor.
- **Maintain a regular pattern of activity.** Don't be frenetic or drive yourself impossibly hard.
- **Do not use alcohol or illicit drugs.** Drugs and alcohol can trigger mood episodes and interfere with the effectiveness of psychiatric medications. You may sometimes find it tempting to use alcohol or illicit drugs to "treat" your own mood or sleep problems—but this almost always makes matters worse. If you have a problem with substances, ask your doctor for help and consider self-help groups such as Alcoholics Anonymous. Be very careful about "everyday" use of small amounts of alcohol, caffeine, and some over-the-counter medications for colds, allergies, or pain. Even small amounts of these substances can interfere with sleep, mood, or your medicine. It may not seem fair that you have to deprive yourself of a cocktail before dinner or a morning cup of coffee, but for many people this can be the "straw that breaks the camel's back."
- **Enlist the support of family and friends.** However, remember that it is not always easy to live with someone who has mood swings. If all of you learn as much as possible about bipolar disorder, you will be better able to help reduce the inevitable stress on relationships that the disorder can cause. Even the "calmest" family will sometimes need outside help dealing with the stress of a loved one who has continued symptoms. Ask your doctor or therapist to help educate both you and your family about bipolar disorder. Family therapy or joining a support group can also be very helpful.
- **Try to reduce stress at work.** Of course, you want to do your very best at work. However, keep in mind that avoiding relapses is more important and will, in the long run, increase your overall productivity. Try to keep predictable hours that allow you to get to sleep at a reasonable time. If mood symptoms interfere with your ability to work, discuss with your doctor whether to "tough it out" or take time off. How much to discuss openly with employers and coworkers is ultimately up to you. If you are unable to work, you might have a family member tell your employer that you are not feeling well and that you are under a doctor's care and will return to work as soon as possible.
- **Learn to recognize the "early warning signs" of a new mood episode.** Early signs of a mood episode differ from person to person and are different for mood elevations and depressions. The better you are at spotting your own early warning signs, the faster you can get help. Slight changes in mood, sleep, energy, self-esteem, sexual interest, concentration, willingness to take on new projects, thoughts of death (or sudden optimism), and even changes in dress and grooming may be early warnings of an impending high or low. *Pay special attention to a change in your sleep pattern,* because this is a common clue that trouble is brewing. Since loss of insight may be an early sign of an impending mood episode, don't hesitate to ask your family to watch for early warnings that you may be missing.
- **Consider entering a clinical study.**

What if you feel like quitting treatment?

It is normal to have occasional doubts and discomfort with treatment. If you feel a treatment is not working or is causing unpleasant side effects, tell your doctor—don't stop or adjust your medication on your own. Symptoms that come back after stopping medication are sometimes much harder to treat. Don't be shy about asking your doctor to arrange for a second opinion if things are not going well. Consultations can be a great help.

How often should I talk with my doctor?

During acute mania or depression, most people talk with their doctor at least once a week, or even every day, to monitor symptoms, medication doses, and side effects. As you recover, contact becomes less frequent; once you are well, you might see your doctor for a quick review every few months.

Regardless of scheduled appointments or blood tests, call your doctor if you have:

- Suicidal or violent feelings
- Changes in mood, sleep, or energy
- Changes in medication side effects
- A need to use over-the-counter medications such as cold medicine or pain medicine
- Acute general medical illnesses or a need for surgery, extensive dental care, or changes in other medicines you take

How can I monitor my own treatment progress?

Keeping a mood chart is a good way to help you, your doctor, and your family manage your disorder. A mood chart is a diary in which you keep track of your daily feelings, activities, sleep patterns, medication and side effects, and important life events. (You can ask your doctor or the NDMDA for a sample chart.) Often just a quick daily entry about your mood is all that is needed. Many people like using a simple, visual scale—from the "most depressed" to the "most manic" you ever felt, with "normal" being in the middle. Noticing changes in sleep, stresses in your life, and so forth may help you identify what are the early warning signs of mania or depression and what types of triggers typically lead to

episodes for you. Keeping track of your medicines over many months or years will also help you figure out which ones work best for you.

What can families and friends do to help?

If you are a family member or friend of someone with bipolar disorder, become informed about the patient's illness, its causes, and its treatments. Talk to the patient's doctor if possible. Learn the particular warning signs for that person which indicate that he or she is becoming manic or depressed. Talk with the person, while he or she is well, about how you should respond when you see symptoms emerging.

- Encourage the patient to stick with treatment, to see the doctor, and to avoid alcohol and drugs. If the patient is not doing well or is having severe side effects, encourage the person to get a second opinion, but ***not*** to stop medication without advice.
- If your loved one becomes ill with a mood episode and suddenly views your concern as interference, remember that this is not a rejection of you but rather a symptom of the illness.
- Learn the warning signs of suicide and take any threats the person makes *very seriously*. If the person is "winding up" his or her affairs, talking about suicide, frequently discussing methods of suicide, or exhibiting increased feelings of despair, step in and seek help from the patient's doctor or other family members or friends. Privacy is a secondary concern when the person is at risk of committing suicide. Call 911 or a hospital emergency department if the situation becomes desperate.
- With someone prone to manic episodes, take advantage of periods of stable mood to arrange "advance directives"—plans and agreements you make with the person when he or she is stable to try to avoid problems during future episodes of illness. You should discuss when to institute safeguards, such as withholding credit cards, banking privileges, and car keys, and when to go to the hospital.
- Share the responsibility for taking care of the patient with other loved ones. This will help reduce the stressful effects that the illness has on caregivers and prevent you from "burning out" or feeling resentful.
- When patients are recovering from an episode, let them approach life at their own pace, and avoid the extremes of expecting too much or too little. Try to do things *with* them, rather than *for* them, so that they are able to regain their sense of self-confidence. Treat people normally once they have recovered, but be alert for telltale symptoms. If there is a recurrence of the illness, you may notice it before the person does. Indicate the early symptoms in a caring manner and suggest talking with the doctor.
- Both you and the patient need to learn to tell the difference between a good day and hypomania, and between a bad day and depression. Patients with bipolar disorder have good days and bad days just like everyone else. With experience and awareness, you will be able to tell the difference between the two.
- Take advantage of the help available from support groups.

PSYCHOTHERAPY

Psychotherapy for bipolar disorder helps a person cope with life problems, come to terms with changes in self-image and life goals, and understand the effects of the illness on significant relationships. As a treatment to relieve symptoms during an acute episode, psychotherapy is much more likely to help with depression than with mania—during a manic episode, patients may find it hard to listen to a therapist. Long-term psychotherapy may help prevent both mania and depression by reducing the stresses that trigger episodes and by increasing patients' acceptance of the need for medication.

Types of psychotherapy

Four specific types of psychotherapy have been studied by researchers. These approaches are particularly useful during acute depression and recovery:

- ***Behavioral therapy*** focuses on behaviors that can increase or decrease stress and ways to increase pleasurable experiences that may help improve depressive symptoms.
- ***Cognitive therapy*** focuses on identifying and changing the pessimistic thoughts and beliefs that can lead to depression.
- ***Interpersonal therapy*** focuses on reducing the strain that a mood disorder may place on relationships.
- ***Social rhythms therapy*** focuses on restoring and maintaining personal and social daily routines to stabilize body rhythms, especially the 24-hour sleep-wake cycle.

Psychotherapy can be individual (only you and a therapist), group (with other people with similar problems), or family. The person who provides therapy may be your doctor or another clinician, such as a social worker, psychologist, nurse, or counselor who works in partnership with your doctor.

How to get the most out of psychotherapy

- Keep your appointments.
- Be honest and open.
- Do the homework assigned to you as part of your therapy.
- Give the therapist feedback on how the treatment is working. Remember that psychotherapy usually works more gradually than medication and may take 2 months or more to show its full effects. However, the benefits may be long lasting. Remember that people can react differently to psychotherapy, just as they do to medicine.

INFORMATION, ADVOCACY, AND RESEARCH

Some of the major organizations that help people with bipolar disorder are listed below. The first 3 are advocacy groups— grassroots organizations founded by patients and families to improve care by providing educational material and support groups, helping with referrals, and working to eliminate stigma and to change laws and policies to benefit individuals with mental illness. The support groups they sponsor provide a forum for mutual acceptance and advice from others who have suffered from severe mood disorders—help that can be invaluable for some individuals. The last 3 organizations, headed by medical researchers, provide education and can help with referrals to programs and clinical studies that provide innovative and state-of-the-art treatment.

National Depressive and Manic-Depressive Association (NDMDA)

- 35,000 members in 250 chapters
- For information:
  730 N. Franklin St., Suite 501
  Chicago IL, 60610-3526
  800-82-NDMDA (800-826-3632)
  www.ndmda.org

National Alliance for the Mentally Ill (NAMI)
- 140,000 members in 1,000 chapters
- For information:
  Colonial Place Three
  2107 Wilson Blvd., Suite 300
  Arlington, VA 22201-3042
  800-950-NAMI (800-950-6264)
  www.nami.org

National Mental Health Association (NMHA)
- 300 chapters
- For information:
  National Mental Health Information Center
  1021 Prince St.
  Alexandria, VA 22314-2971
  800-969-6642
  www.nmha.org

National Foundation for Depressive Illness, Inc. (NFDI)
PO Box 2257
New York, NY 10116-2257
800-248-4344

Madison Institute of Medicine
- Home of the *Lithium Information Center* and the *Stanley Center for the Innovative Treatment of Bipolar Disorder*
- Distributes very useful consumer guides to mood stabilizers
  7617 Mineral Point Rd., Suite 300
  Madison, WI 53717
  608-827-2470
  www. healthtechsys.com/mim.html

Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)
- Project that is conducting studies involving 5,000 bipolar patients treated in different centers in the United States. The goal is to improve effectiveness of treatment for bipolar disorder. If you are interested in participating, visit:
  www.edc.gsph.pitt.edu/stepbd

FOR MORE INFORMATION

The NDMDA distributes free the booklet *A Guide to Depressive and Manic-Depressive Illness: Diagnosis, Treatment and Support*, along with a NDMDA bookstore catalog and chapter directory. The publications listed below also provide more information on bipolar disorder. Most are available from the NDMDA bookstore. To order these materials, call 800-82-NDMDA.

Medical information about bipolar disorder:

The Bipolar Child: the Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder. Demitri F. Papolos and Janice Papolos. Broadway Books, 1999.

Cognitive-Behavioral Therapy for Bipolar Disorder. MR Basco and AJ Rush. Guilford, 1996.

The Depression Workbook: a Guide for Living With Depression and Manic Depression. Mary Ellen Copeland, MS. Newharbinger Publications, 1992.

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). American Psychiatric Association, 1994.

Everyone Needs a Hand to Hold on to (18-minute video produced for NDMDA; comes with a discussion guide), 1995.

Living With Manic-Depressive Illness: a Guidebook for Patients, Families and Friends. NDMDA, 1997. Comprehensive, fully updated 60-page guide to the illness.

Manic-Depressive Illness. Frederick K. Goodwin, MD, and Kay Redfield Jamison, PhD. Oxford University Press, 1990.

A Mood Apart: Depression, Mania, and Other Afflictions of the Self. Peter C. Whybrow, MD. Basic Books, 1997.

Mood Genes: Hunting for Origins of Mania and Depression. Samuel H. Barondes, MD. W.H. Freeman and Co, 1998

Night Falls Fast: Understanding Suicide. Kay Redfield Jamison, PhD. Alfred A. Knopf, 1999.

Restoring Intimacy: the Patient's Guide to Maintaining Relationships During Depression. NDMDA developed this book to cover difficult and real issues for people living with depression. NDMDA, 1999.

Structured Group Psychotherapy for Bipolar Disorder: the Life Goals Program. M Bauer and L McBride. Springer, 1996.

Touched With Fire: Manic-Depressive Illness and the Artistic Temperament. Kay Redfield Jamison. Simon & Schuster, 1996.

When Someone You Love Is Depressed: How to Help Your Loved One Without Losing Yourself. Laura Epstein Rosen, PhD, and Xavier Francisco Amador, PhD. Simon & Schuster, revised 1997.

Outstanding books by people with bipolar disorder or depression:

The Beast: a Reckoning With Depression. Tracy Thompson. G.P. Putnam's Sons, 1995.

A Brilliant Madness: Living With Manic-Depressive Illness. Patty Duke and Gloria Hockman. Bantam Books, 1992.

Call Me Anna: the Autobiography of Patty Duke. Patty Duke and Kenneth Turan. Bantam, 1987.

Darkness Visible, a Memoir of Madness. William Styron. Random House, 1990.

On the Edge of Darkness: Conversations About Conquering Depression. Kathy Cronkite. Doubleday, 1994.

An Unquiet Mind, a Memoir of Moods and Madness. Kay Redfield Jamison, PhD. Random House, 1996.

Undercurrents: a Therapist's Reckoning With Her Own Depression. Martha Manning. Harper Collins, 1994.

FOR MORE INFORMATION

To request more copies of this handout, please contact NDMDA or NAMI (see above).

The recommendations in this article were based on a recent survey of experts on the medication treatment of bipolar disorder (published as A Postgraduate Medicine Special Report, April 2000). You can download an Adobe Acrobat file of this study and this guide for patients and families at our website:

www.psychguides.com

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