The Expert Consensus Guidelines for Treating Depression in Bipolar Disorder

Allen J. Frances, M.D., David A. Kahn, M.D., Daniel Carpenter, Ph.D., John P. Docherty, M.D., and Stacy L. Donovan

We present expert consensus guideline recommendations for the treatment of bipolar depression. These were arrived at through the statistical aggregation of the survey responses of 61 leading clinical researchers to eight questions about the key decision points in the management of bipolar depression. The experts' first-line recommendation for treating psychotic depression in bipolar disorder is to provide a combination of mood stabilizer, antidepressant, and neuroleptic medication. For severe, but nonpsychotic bipolar depression, the experts recommend the combination of a mood stabilizer and an antidepressant. For milder bipolar depression, a mood stabilizer and an antidepressant together or a mood stabilizer alone would be first line. The experts' antidepressant dose and dosing schedule recommendations are equivalent for unipolar and bipolar depression, but the experts recommend a faster discontinuation of antidepressants during the maintenance phase in bipolar patients—probably to reduce the risk of rapid cycling. Among the antidepressants, the experts prefer bupropion and the serotonin reuptake inhibitors as first line. They also believe that bupropion is least likely among antidepressants to cause switches to mania. Among mood stabilizers, the experts rate lithium as most likely to have a direct antidepressant effect.
(J Clin Psychiatry 1998;59[suppl 4]:73–79)

We have three purposes in this paper. First, we will describe our new Expert Consensus Guideline method to develop treatment recommendations for a number of psychiatric disorders. Next, we will explain why this method is particularly necessary in establishing guidelines for treating depression in bipolar disorder. Finally, we will present the results of survey responses from 61 experts in bipolar disorder on questions covering a number of the crucial decision points in the treatment of bipolar depression.

Our Expert Consensus Guideline method allows us to address the complexities and multiple contingencies that commonly arise in the treatment of patients with bipolar depression. The overall method has been presented in considerable detail by Frances et al.[1] We will briefly describe the approach here in order to help the reader understand the context in which the expert survey results for bipolar depression were gathered. Our method takes as its starting point, and then builds upon, the existing guidelines for treating psychiatric disorders that are based upon the available scientific literature. We go beyond what is available in existing guidelines by providing expert recommendations for the many clinical questions that have not yet been addressed in controlled research. The guideline recommendations emerge from a statistical aggregation of responses to survey questions obtained from a large group (usually 60–100) of the leading experts on the given disorder. This survey method allows us to identify expert recommendations on treatment options for specific clinical scenarios in those areas for which the research literature provides insufficient guidance.

Our survey questions are directed toward providing detailed guidance on the key decision points in treatment. We survey and compare the answers of two different groups of practitioners with quite divergent previous career experiences: (1) academic experts who are active researchers contributing to the literature on the given diagnosis and (2) busy clinical practitioners who do no research but see lots of patients with the problem. Through the systematic statistical analysis of the responses, we are able to present a clear, quantitative, and easy to use summary of the most highly regarded treatment options for a given clinical situation. The respondents rank their recommended treatments according to their expected efficacy with actual patients seen in their clinical practice. A major value of our method of establishing guidelines is that it enables practitioners to take advantage of the knowledge and experience of the leading experts in our field as they tackle the most difficult questions in patient management.

From the Departments of Psychiatry, Duke University Medical Center, Durham, N.C. (Dr. Frances), Columbia University (Dr. Kahn), and Cornell University (Drs. Carpenter and Docherty and Ms. Donovan), New York, N.Y.

Presented at the symposium "Beyond SSRIs," held January 3–4, 1997, Buckhead, Ga., which was supported by an unrestricted educational grant from Glaxo Wellcome.

Reprint requests to: Allen J. Frances, M.D., Duke University Medical Center, Box 3950, Durham, NC 27710.

For a variety of reasons, this type of expert consensus approach is especially necessary to develop the treatment recommendations that will assist clinicians in managing bipolar depression. Despite the fact that bipolar disorder occurs in 1%–3% of the general population and is frequently encountered in clinical practice, researchers have, with very few exceptions, tended to avoid studying it and instead have focused a great deal of attention on unipolar depression. This is unfortunate because patients with bipolar disorder are at a relatively high risk for suicide, rapid cycling, frequent hospitalizations, other complications, and high treatment cost.

The paucity of research on bipolar disorder is undoubtedly attributable to the many special and difficult challenges it poses to the design of well-controlled studies. Research designs for studying bipolar depression are necessarily more complicated than the study designs that have become almost an industry standard for unipolar depression. First, medication protocols for bipolar disorder are necessarily complex. Patients with bipolar depression are usually (but not always) already taking one or another mood-stabilizing drug in addition to antidepressant medication. This problem is exacerbated by the fact that several different mood-stabilizing drugs, alone or in combination, may be used in treating bipolar disorder and that many patients may also be taking adjunctive neuroleptic or anxiolytic medication. A wide variety of antidepressants, alone and in combination, are also available for treating bipolar depression, and the systematic study of all of the possibly plausible medication combinations for bipolar depression would probably require more than a thousand design permutations. Another obstacle to systematic research is the difficulty of controlling for the great heterogeneity in the natural course of bipolar disorder. Patients vary greatly in their age at onset, the frequency and types of episodes, typical duration of episodes, tendency toward switches, and in their proportion of highs and lows.

Finally, the behavioral characteristics of patients with bipolar disorder have made this disorder a special challenge for researchers. When these patients are mood elevated or irritable, they may be difficult to recruit and maintain in research studies. Moreover, the risks of hospitalization, suicide, and causing highs have made these patients somewhat less attractive for research, particularly for those studies that are industry funded. There are also concerns that rapid cycling can develop as a result of chasing depression too aggressively with antidepressants. The aggregation of all of these factors complicating research on bipolar depression has resulted in our having an enormous literature on unipolar depression (because this is much less difficult to study) and an insufficient literature on bipolar depression.

Our Expert Consensus Guideline method is intended to aggregate the best expert opinion available on bipolar depression in order to fill in the gaps that have been left unaddressed by the incomplete literature in this area.[1]

METHOD

We initially developed a preliminary treatment algorithm based on the very well done American Psychiatric Association guideline for bipolar disorder.[2] We then focused on the key decision points that frequently arise in clinical practice with bipolar patients for which the literature is incomplete and the American Psychiatric Association guideline insufficiently specific. An 81-item questionnaire was created, with each question posed in the form of a hypothetical clinical situation in the assessment or treatment of bipolar disorder. The questionnaire (in two parts) was sent to 68 leading experts on bipolar disorder, and, remarkably enough, 61 (90%) of them responded—assuring that the results are highly representative. The experts included individuals involved in recent research publications and funded grants, the DSM-IV advisers for mood disorders, the Task Force for the American Psychiatric Association's Practice Guideline for the Treatment of Patients With Bipolar Disorder, and individuals who have worked on other mood disorder guidelines.

The experts were instructed to rate the appropriateness of each treatment option using a 9-point scale modified from the RAND corporation method[3]:

9 = extremely appropriate—this is your treatment of choice (may have more than one per question);
7–8 = appropriate—a first line treatment you would often use;
4–6 = equivocal—a second line treatment you would sometimes use (e.g., after first line had failed);
2–3 = usually inappropriate—at most, a third line treatment you would rarely use;
1 = extremely inappropriate—a treatment you would never use.[4]

A portion of the questionnaire was also completed by 165 busy clinicians who do not do research but who do treat a large number of bipolar patients. It was gratifying that researchers and clinicians showed a high rate of agreement, validating that the opinions of the experts are relevant to general clinical practice and are not limited in their applicability to the possibly hothouse atmosphere of university research centers.

A quantitative statistical analysis was performed on the survey responses, and the results of these analyses are displayed graphically on bar charts and in tables of numerical values in the Results section. The mean (Avg), standard deviation (SD), distributions, and confidence intervals (CI) were calculated for each question. The 95% confidence interval bars indicate, for each answer to each question, the range within which there is a 95% chance that the

mean would fall if the question were asked of a different, but similarly selected, group of experts. A narrow bar suggests that the results are robust and replicable. When the bars for the different options do not overlap, this means that there is a statistically significant difference between the treatment choices.

We designated a categorical rating of first, second, or third line for each item based on the category into which the 95% CI of its mean score fell. First line treatments are those strategies that the experts believe are appropriate as initial treatments for a given scenario. To be rated a first line treatment, the lower end of the CI bar had to fall at, or above, a score of 6.5. A first line treatment recommendation that achieves a rating of "9" by at least half of the experts has the special designation of "Treatment of Choice." To be rated second line, the CI had to fall between 3.5 and 6.49. For certain questions, the experts did not reach a consensus on first line options, and instead the high second line ratings dominated. In order to distinguish among choices in these scenarios, we labeled those items where the CIs overlapped with the first line category as "top-tier second line." Second line treatments are the experts' preferred choice for patients who do not respond adequately to, or cannot tolerate, the first line treatment. Alternatively, a second line choice may be the best option if the first line treatment is unsuitable for a particular patient for a variety of reasons, such as patient preference, poor previous response, problematic side effects, potential drug interaction, or general medical contraindication. Third line treatments are those options the experts believe are most often either last resort or clearly inappropriate, to be used only when other recommended alternatives have not been efficacious. To qualify as a third line treatment, a portion of the CI had to fall below 3.5. A rating of "No Consensus" was designated when the distribution of expert responses did not significantly differ from a chance distribution as determined by a chi-square test.

We established a priori criteria to determine what ratings are defined as first, second, and third line treatments across all of our Expert Consensus Guideline series to eliminate the risk of potential bias in interpretation. In rating each item, we consistently assigned the lowest rating into which the CI fell in an effort to avoid chance upgrading. All the raw data for each question are presented so that the steps in translation from expert survey responses to guideline recommendations are clear.[4] We will now present the results to the eight questions on the survey that dealt specifically with the treatment of bipolar depression.

RESULTS

The results section for this paper is reprinted from the *Journal of Clinical Psychiatry*, Volume 57, Supplement 12A, 1996, pages 49–53.[4]

DISCUSSION

The Expert Consensus recommendations for bipolar depression mirror the existing literature on unipolar depression but, in addition, emphasize the need to avoid the risks of rapid cycling and switches to mania. For bipolar depression with psychosis, the experts recommend either electroconvulsive therapy (ECT) or a combination of mood stabilizer, antidepressant, and neuroleptic. ECT has the fastest and probably the highest response rates, but also has the disadvantages of relatively high relapse rates and of being relatively uninformative about what medication treatment would be most helpful in the continuation and maintenance phases. The combination of antidepressants and neuroleptics is far more effective than either alone for treating psychotic depression, but in bipolar patients requires additional coverage with a mood stabilizer to reduce the risks of rapid cycling and switches.

The first line recommendation for bipolar depression, when it is severe, but nonpsychotic, is a mood stabilizer plus an antidepressant. This recommendation again indicates that antidepressants alone should not be given for bipolar depression. For milder bipolar depression, the experts recommend either mood stabilizer plus antidepressant, or mood stabilizer alone (this latter option is probably also an effort to reduce the risk consequent to antidepressant exposure).

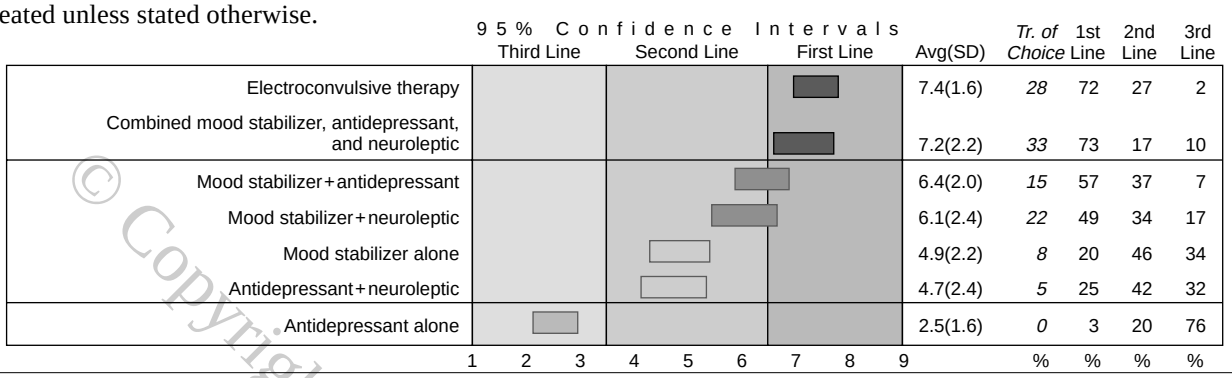
When asked to rate from among the many antidepressants available, the experts preferred bupropion and the serotonin reuptake inhibitors. They also rated bupropion as the least likely to cause a switch to mania or rapid cycling. It is of interest that most experts avoid the use of standard tricyclic antidepressants in bipolar depression.

The experts usually titrate the dosage of antidepressant upward to the same dose and at the same rate as they would when treating unipolar depression. Likewise, they would continue the acute trial for 6 to 12 weeks, as they would when treating unipolar depression. However, the experts were more likely to taper the antidepressant more quickly in bipolar depression than would be the case in treating unipolar depression—again to reduce the risks of antidepressant exposure in order to prevent rapid cycling. Among the mood stabilizers, the experts rate lithium as the most likely to have a direct antidepressant effect.

It is also important to recognize that appropriately using any guideline for treating a particular disorder requires making the right diagnosis in the first place. This is particularly true for bipolar disorder, which is often underdiagnosed in clinical practice. When severe, bipolar disorder is often missed and confused with schizophrenia. At the bipolar II end, with fewer or less clear-cut highs, it is often confused with unipolar depression. Patients with psychotic mania or psychotic depression as part of bipolar disorder are often misdiagnosed as having schizophrenia. Perhaps even more frequently, patients are given

1 Please rate each of the following for the acute treatment of a patient who has bipolar I depression with psychosis. In this and following questions about acute depression, assume the patient is currently untreated unless stated otherwise.

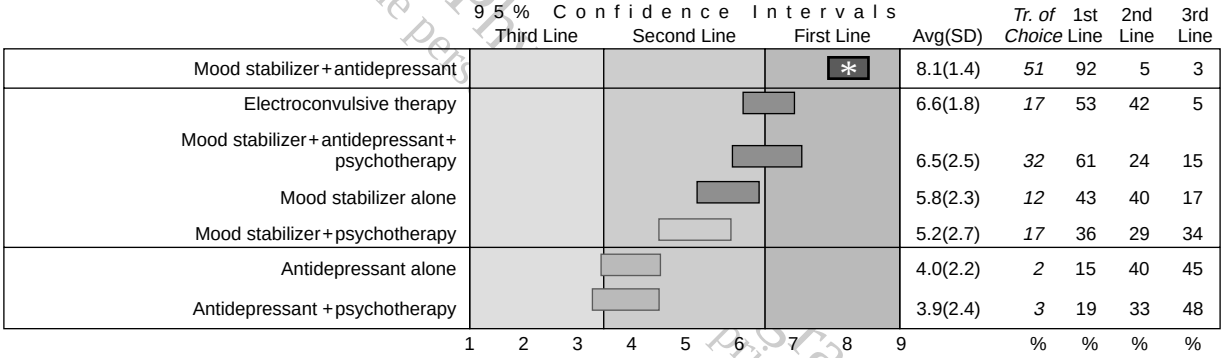
Comment: Because psychotic depression is potentially life-threatening, the experts recommend starting with a potent and definitive first line treatment (ECT or combined mood stabilizer, antidepressant, and neuroleptic), rather than building up from less intensive approaches. A less intensive treatment should be considered only when there are contraindications to the first line treatments (e.g., tardive dyskinesia). Note that antidepressants alone are to be avoided.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Electroconvulsive therapy	7.4(1.6)	*28*	72	27	2
Combined mood stabilizer, antidepressant, and neuroleptic	7.2(2.2)	*33*	73	17	10
Mood stabilizer + antidepressant	6.4(2.0)	*15*	57	37	7
Mood stabilizer + neuroleptic	6.1(2.4)	*22*	49	34	17
Mood stabilizer alone	4.9(2.2)	*8*	20	46	34
Antidepressant + neuroleptic	4.7(2.4)	*5*	25	42	32
Antidepressant alone	2.5(1.6)	*0*	3	20	76
		%	%	%	%

2 Please rate each of the following for the acute treatment of a patient with bipolar I depression that is severe but nonpsychotic.

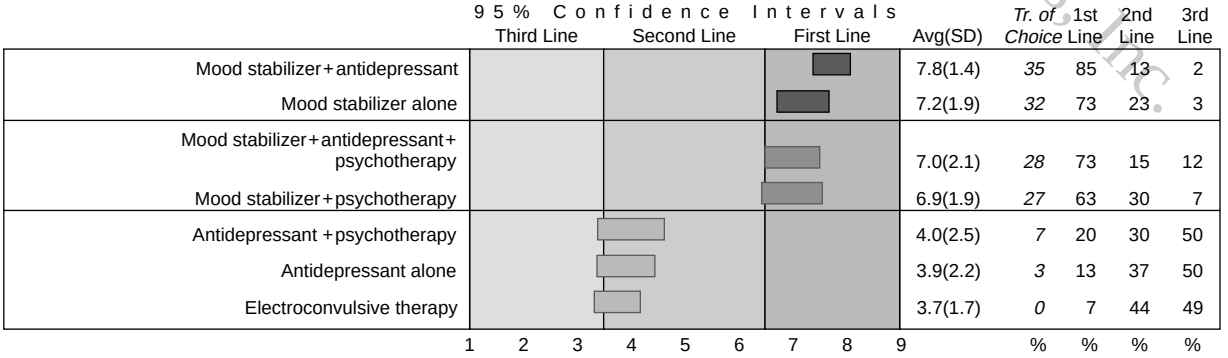
Comment: The treatment of bipolar depression without psychosis is different than when psychotic features are present. Neuroleptics are generally avoided (see Question 25). ECT is less likely and psychotherapy more likely to be used. An antidepressant combined with a mood stabilizer is first line. Psychotherapy plays a second line role as an adjunct to medication. Please note again that treatments without mood stabilizers (antidepressants with or without psychotherapy) are not recommended.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Mood stabilizer + antidepressant	8.1(1.4)	*51*	92	5	3
Electroconvulsive therapy	6.6(1.8)	*17*	53	42	5
Mood stabilizer + antidepressant + psychotherapy	6.5(2.5)	*32*	61	24	15
Mood stabilizer alone	5.8(2.3)	*12*	43	40	17
Mood stabilizer + psychotherapy	5.2(2.7)	*17*	36	29	34
Antidepressant alone	4.0(2.2)	*2*	15	40	45
Antidepressant + psychotherapy	3.9(2.4)	*3*	19	33	48
		%	%	%	%

3 Please rate each of the following for the acute treatment of a patient with milder bipolar I depression.

Comment: For milder bipolar I depression, the experts recommend a mood stabilizer either combined with an antidepressant or given alone. This is in contrast to the recommendation for severe bipolar depression, in which the only first line recommendation is for a mood stabilizer plus antidepressant. The difference probably reflects the desire to avoid the risks of antidepressant-induced cycling, especially in the mildly depressed patient when the need for relief is less desperate. The addition of psychotherapy to either drug regimen plays an important role though it falls just short of first line status. Once again, plans that omit a mood stabilizer are not recommended.

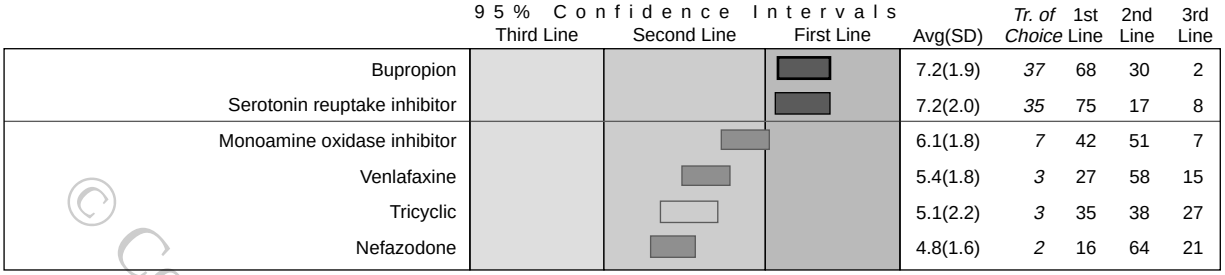


	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Mood stabilizer + antidepressant	7.8(1.4)	*35*	85	13	2
Mood stabilizer alone	7.2(1.9)	*32*	73	23	3
Mood stabilizer + antidepressant + psychotherapy	7.0(2.1)	*28*	73	15	12
Mood stabilizer + psychotherapy	6.9(1.9)	*27*	63	30	7
Antidepressant + psychotherapy	4.0(2.5)	*7*	20	30	50
Antidepressant alone	3.9(2.2)	*3*	13	37	50
Electroconvulsive therapy	3.7(1.7)	*0*	7	44	49
		%	%	%	%

* = *Treatment of choice;* ☐ = *No Consensus* *Note: 1st Line percentage includes Treatment of Choice percentage.*

4 For severe bipolar I or II depression, please rank the following antidepressants in the order you would actually use them.

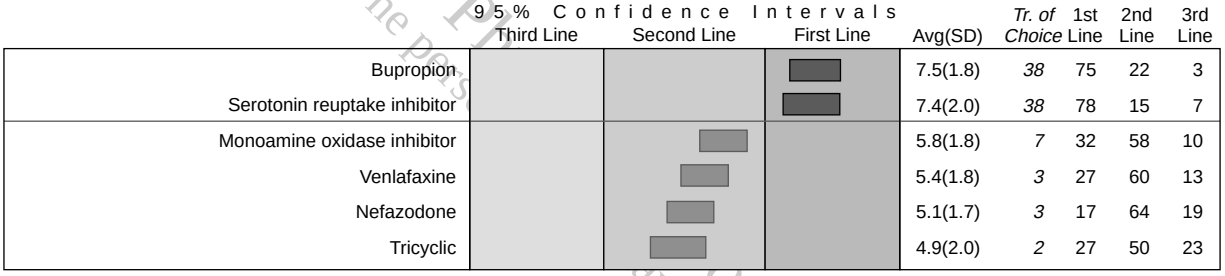
Comment: For severe bipolar depression, the experts select bupropion and serotonin reuptake inhibitors as first line treatments. Although not selected as first line, monoamine oxidase inhibitors appear to be preferred to traditional tricyclics. The role of the newer antidepressants has not been established.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Bupropion	7.2(1.9)	*37*	68	30	2
Serotonin reuptake inhibitor	7.2(2.0)	*35*	75	17	8
Monoamine oxidase inhibitor	6.1(1.8)	*7*	42	51	7
Venlafaxine	5.4(1.8)	*3*	27	58	15
Tricyclic	5.1(2.2)	*3*	35	38	27
Nefazodone	4.8(1.6)	*2*	16	64	21
		%	%	%	%

5 For milder bipolar depression, please rank the antidepressants in the order you would actually use them.

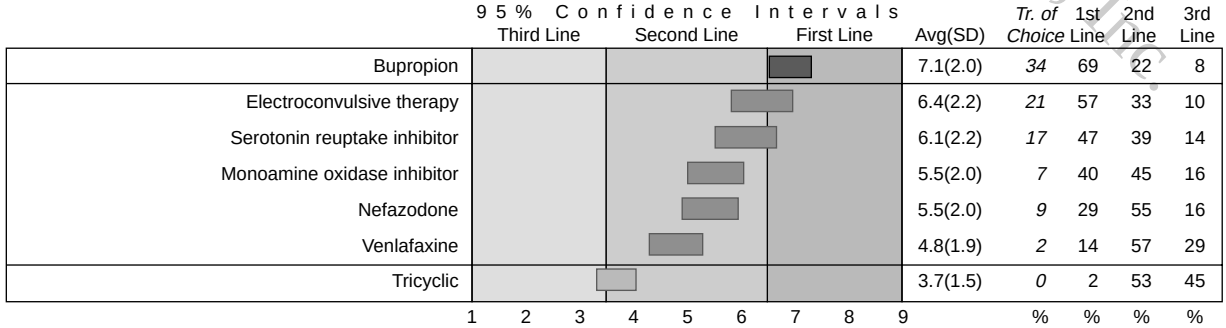
Comment: The results for milder bipolar depression are essentially the same as for severe depression, except for a less clear preference for monoamine oxidase inhibitors among the second line choices.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Bupropion	7.5(1.8)	*38*	75	22	3
Serotonin reuptake inhibitor	7.4(2.0)	*38*	78	15	7
Monoamine oxidase inhibitor	5.8(1.8)	*7*	32	58	10
Venlafaxine	5.4(1.8)	*3*	27	60	13
Nefazodone	5.1(1.7)	*3*	17	64	19
Tricyclic	4.9(2.0)	*2*	27	50	23
		%	%	%	%

6 Please rate the degree to which each of the following is likely to avoid switching patients into mania or accelerated cycling (i.e., the least likely to cause a switch is the most appropriate).

Comment: While all antidepressants can induce mania, the antidepressant treatment most recommended to avoid mania is bupropion. The tricyclic antidepressants are not recommended when a switch to mania or accelerated cycling is a concern.

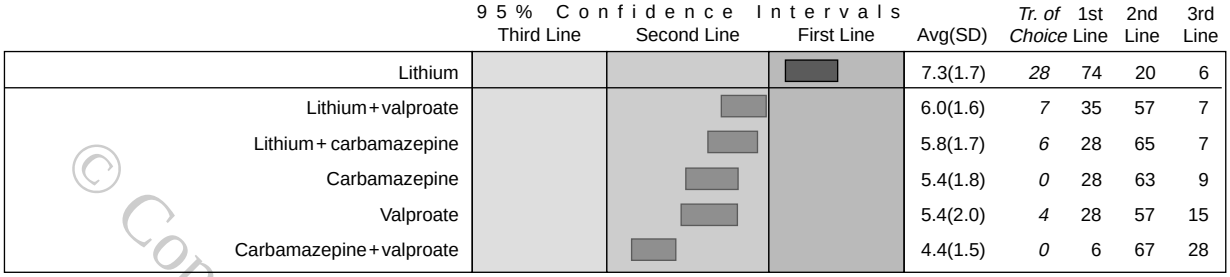


	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Bupropion	7.1(2.0)	*34*	69	22	8
Electroconvulsive therapy	6.4(2.2)	*21*	57	33	10
Serotonin reuptake inhibitor	6.1(2.2)	*17*	47	39	14
Monoamine oxidase inhibitor	5.5(2.0)	*7*	40	45	16
Nefazodone	5.5(2.0)	*9*	29	55	16
Venlafaxine	4.8(1.9)	*2*	14	57	29
Tricyclic	3.7(1.5)	*0*	2	53	45
		%	%	%	%

* = *Treatment of choice;* = *No Consensus* *Note: 1st Line percentage includes Treatment of Choice percentage.*

7 Please rate each of the following mood stabilizer regimens, if you had to use it alone, without other medications, in order to achieve direct antidepressant effects in nonpsychotic bipolar depression.

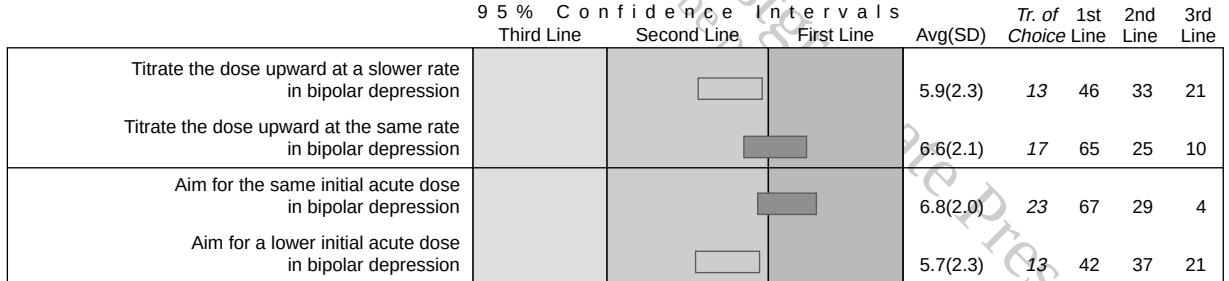
Comment: To achieve direct antidepressant effects with a mood stabilizer alone, lithium monotherapy is the only first line recommendation. While recent reports cast doubt on earlier studies demonstrating good antidepressant effects for lithium, the other mood stabilizers were judged even weaker for this use.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Lithium	7.3(1.7)	*28*	74	20	6
Lithium + valproate	6.0(1.6)	*7*	35	57	7
Lithium + carbamazepine	5.8(1.7)	*6*	28	65	7
Carbamazepine	5.4(1.8)	*0*	28	63	9
Valproate	5.4(2.0)	*4*	28	57	15
Carbamazepine + valproate	4.4(1.5)	*0*	6	67	28
		%	%	%	%

8 Compared with your practice for non-bipolar depression, please rate each method of prescribing antidepressants for bipolar depression in a non–rapid cycler. Assume you are also using a mood stabilizer.

Comment: Antidepressant dosing schemes and durations of continuation treatment have been studied extensively in non-bipolar major depression, but hardly at all in bipolar depression. Some textbooks suggest "lower and slower" approaches in bipolar disorder. The experts clearly support a first line acute strategy of giving the same maximum doses to treatment-resistant patients, for a comparable duration. (We used 6–12 weeks only as an example, based on the guidelines for depression from the federal Agency for Health Care Policy and Research. Other sources suggest 4–8 weeks.) As for the rate of increasing the initial dose, there was strong second line support for increasing the dose as quickly as one would in non-bipolar depression, and aiming for the same initial target dose. Note that lack of first line strength reflects the preference of some experts for the "lower and slower" approach at first, though nearly all would eventually be aggressive in pursuing an adequate trial. Following acute symptom remission in non-bipolar major depression, continuation treatment of single episodes typically lasts 6–12 months, and lifetime prophylaxis is often advised after several episodes. These durations appear less applicable in bipolar depression, where top-tier second line support was given to tapering the medication more quickly after the episode resolves, presumably to lessen the risk of inducing cycling.



	Avg(SD)	*Tr. of Choice*	1st Line	2nd Line	3rd Line
Titrate the dose upward at a slower rate in bipolar depression	5.9(2.3)	*13*	46	33	21
Titrate the dose upward at the same rate in bipolar depression	6.6(2.1)	*17*	65	25	10
Aim for the same initial acute dose in bipolar depression	6.8(2.0)	*23*	67	29	4
Aim for a lower initial acute dose in bipolar depression	5.7(2.3)	*13*	42	37	21
In treatment-resistant bipolar depression, use the same maximum dose as in non-bipolar	8.1(1.3)	*48*	92	6	2
In treatment-resistant bipolar depression, use lower maximum doses	4.1(1.8)	*0*	10	42	48
Continue an acute trial for as long in bipolar as in non-bipolar depression (e.g., 6–12 weeks)	7.3(1.8)	*31*	77	17	6
Acute trials should be shorter in bipolar depression	4.9(2.3)	*12*	23	42	35
After response in bipolar depression, continue drug for as long as in non-bipolar (e.g., 6–12 mos)	5.7(2.3)	*15*	35	44	21
After response in bipolar depression, taper the antidepressant more quickly	6.4(2.3)	*18*	63	22	16
		%	%	%	%

* = *Treatment of choice;* □ = *No Consensus* *Note: 1st Line percentage includes Treatment of Choice percentage.*

antidepressants for what appears to be unipolar depression, without a careful evaluation of the possible history of manic or hypomanic episodes or a family history of bipolar disorder. It should also be noted that thorough diagnostic evaluation often requires the presence of an informant who knows the patient well. Patients with bipolar disorder are often lacking in insight about their condition and do not always make very good historians.

Although these recommendations represent the best and current expert consensus opinion, we should also recognize their limitations. Throughout the history of medicine, experts have often been wrong. Our confidence in these recommendations will grow more certain only upon their being tested by systematic research. Each of the questions raised in the survey represents a topic for future research, which is especially necessary in the area of bipolar depression. In the meantime, we plan to repeat the Expert Consensus Guidelines for bipolar disorder at 2-year intervals so as to update them through the accumulation of new research. These guidelines are already forming the basis for standardization of care delivery in many state, federal, and managed care systems. Expert Consensus Guidelines are also available for schizophrenia, obsessive-compulsive disorder, and agitation.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), nefazodone (Serzone), venlafaxine (Effexor).

REFERENCES

1. Frances AJ, Kahn DA, Carpenter D, et al. The Expert Consensus Practice Guideline Project: a new method of establishing best practice. Journal of Practical Psychiatry and Behavioral Health 1996;2:295–306
2. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Bipolar Disorder. Washington, DC: American Psychiatric Association; 1994
3. Brook RH, Chassin MR, Fink A, et al. A method for the detailed assessment of appropriateness of medical technologies. Int J Technol Assess Health Care 1986;2:53–63
4. Frances AJ, Docherty JP, Kahn DA. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder. J Clin Psychiatry 1996;57(suppl 12A):1–88