

Brief Summary

GUIDELINE TITLE

Practice guideline for the treatment of patients with bipolar disorder (revision).

BIBLIOGRAPHIC SOURCE(S)

- Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002 Apr;159(4 Suppl):1-50. [472 references] [PubMed](#)

GUIDELINE STATUS

According to the guideline developer, this guideline is still considered to be current as of November 2005. A Guideline Watch, which summarizes significant developments in practice since the publication of the original guideline, was published in November 2005 and is available from the [American Psychiatric Association Web site](#) (see also the "Availability of Companion Documents" field below).

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [October 25, 2006, Effexor \(venlafaxine HCl\)](#): Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcome.
- [September 29, 2006, Lamictal \(lamotrigine\)](#): New preliminary information available regarding the effects of Lamictal on the baby if taken during the first three months of pregnancy.
- [May 12, 2006, Paxil \(paroxetine\) and Paxil CR](#): Changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information related to adult patients, particularly those who are younger adults.
- [January 13, 2006, Clozaril \(clozapine\) tablets](#): Revisions to the BOXED WARNING, WARNINGS, CONTRAINDICATIONS, PRECAUTIONS (Information for Patients and Pharmacokinetic-Related Interactions subsections), and ADVERSE REACTIONS (Postmarketing Clinical Experience subsection) sections of the prescribing information.
- [December 8, 2005, Paxil \(paroxetine\)](#): Pregnancy category changed from C to D and new data and recommendations added to the WARNINGS section of prescribing information.
- [September 27, 2005, Paxil \(paroxetine\) and Paxil CR](#): Changes to the Pregnancy/PRECAUTIONS section of the Prescribing Information to describe the results of a retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy.
- [July 1, 2005, Antidepressants](#): Public Health Advisory issued to update patients and healthcare providers in response to recent scientific publications that report the possibility of increased risk of suicidal behavior in adults treated with antidepressants.

- [April 19, 2005, Trileptal \(oxcarbazepine\)](#): Revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information. The updated WARNINGS section describes serious dermatological reactions in children and adults, and the PRECAUTIONS section has been updated to include language regarding multi-organ hypersensitivity reactions.

BRIEF SUMMARY CONTENT

**** REGULATORY ALERT ****

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RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence regarding the recommendation.

Definition of grades of recommendation [I-III] are presented at the end of the "Major Recommendations" field.

Psychiatric Management

At this time, there is no cure for bipolar disorder; however, treatment can decrease the associated morbidity and mortality [I]. Initially, the psychiatrist should perform a diagnostic evaluation and assess the patient's safety and level of functioning to arrive at a decision about the optimum treatment setting [I]. Subsequently, specific goals of psychiatric management include establishing and maintaining a therapeutic alliance, monitoring the patient's psychiatric status, providing education regarding bipolar disorder, enhancing treatment compliance, promoting regular patterns of activity and of sleep, anticipating stressors, identifying new episodes early, and minimizing functional impairments [I].

Acute Treatment

Manic or Mixed Episodes

The first-line pharmacological treatment for more severe manic or mixed episodes is the initiation of either lithium plus an antipsychotic or valproate plus an antipsychotic [I]. For less ill patients, monotherapy with lithium, valproate, or an antipsychotic such as olanzapine may be sufficient [I]. Short-term adjunctive treatment with a benzodiazepine may also be helpful [II]. For mixed episodes, valproate may be preferred over lithium [II]. Atypical antipsychotics are preferred over typical antipsychotics because of their more benign side effect profile [I], with most of the evidence supporting the use of olanzapine or risperidone [III]. Alternatives include carbamazepine or oxcarbazepine in lieu of lithium or valproate [II]. Antidepressants should be tapered and discontinued if

possible [I]. If psychosocial therapy approaches are used, they should be combined with pharmacotherapy [I].

For patients who, despite receiving maintenance medication treatment, experience a manic or mixed episode (i.e., a "breakthrough" episode), the first-line intervention should be to optimize the medication dose [I]. Introduction or resumption of an antipsychotic is sometimes necessary [III]. Severely ill or agitated patients may also require short-term adjunctive treatment with a benzodiazepine [I].

When first-line medication treatment at optimal doses fails to control symptoms, recommended treatment options include addition of another first-line medication [I]. Alternative treatment options include adding carbamazepine or oxcarbazepine in lieu of an additional first-line medication [III], adding an antipsychotic if not already prescribed [I], or changing from one antipsychotic to another [III]. Clozapine may be particularly effective in the treatment of refractory illness [II]. Electroconvulsive therapy may also be considered for patients with severe or treatment-resistant mania or if preferred by the patient in consultation with the psychiatrist [I]. In addition, electroconvulsive therapy is a potential treatment for patients experiencing mixed episodes or for patients experiencing severe mania during pregnancy [II].

Manic or mixed episodes with psychotic features usually require treatment with an antipsychotic medication [II].

Depressive Episodes

The first-line pharmacological treatment for bipolar depression is the initiation of either lithium [I] or lamotrigine [II]. Antidepressant monotherapy is not recommended [I]. As an alternative, especially for more severely ill patients, some clinicians will initiate simultaneous treatment with lithium and an antidepressant [III]. In patients with life-threatening inanition, suicidality, or psychosis, electroconvulsive therapy also represents a reasonable alternative [I]. Electroconvulsive therapy is also a potential treatment for severe depression during pregnancy [II].

A large body of evidence supports the efficacy of psychotherapy in the treatment of unipolar depression [I]. In bipolar depression, interpersonal therapy and cognitive behavior therapy may be useful when added to pharmacotherapy [II]. While psychodynamic psychotherapy has not been empirically studied in patients with bipolar depression, it is widely used in addition to medication [III].

For patients who, despite receiving maintenance medication treatment, suffer a breakthrough depressive episode, the first-line intervention should be to optimize the dose of maintenance medication [II].

When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment at optimal doses, next steps include adding lamotrigine [I], bupropion [II], or paroxetine [II]. Alternative next steps include adding other newer antidepressants (e.g., a selective serotonin reuptake inhibitor [SSRI] or venlafaxine) [II] or a monoamine oxidase inhibitor (MAOI) [II]. For patients with severe or treatment-

resistant depression or depression with psychotic or catatonic features, electroconvulsive therapy should be considered [I].

The likelihood of antidepressant treatment precipitating a switch into a hypomanic episode is probably lower in patients with bipolar II depression than in patients with bipolar I depression. Therefore, clinicians may elect to recommend antidepressant treatment earlier in patients with bipolar II disorder [II].

Depressive episodes with psychotic features usually require adjunctive treatment with an antipsychotic medication [I]. Electroconvulsive therapy (ECT) represents a reasonable alternative [I].

Rapid Cycling

As defined in DSM-IV-TR and applied in this guideline, rapid cycling refers to the occurrence of four or more mood disturbances within a single year that meet criteria for a major depressive, mixed, manic, or hypomanic episode. These episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity (e.g., from a major depressive to a manic episode). The initial intervention in patients who experience rapid cycling is to identify and treat medical conditions, such as hypothyroidism or drug or alcohol use, that may contribute to cycling [I]. Certain medications, particularly antidepressants, may also contribute to cycling and should be tapered if possible [II]. The initial treatment for patients who experience rapid cycling should include lithium or valproate [I]; an alternative treatment is lamotrigine [I]. For many patients, combinations of medications are required [II].

Maintenance Treatment

Following remission of an acute episode, patients may remain at particularly high risk of relapse for a period of up to 6 months; this phase of treatment, sometimes referred to as continuation treatment, is considered in this guideline to be part of the maintenance phase. Maintenance regimens of medication are recommended following a manic episode [I]. Although few studies involving patients with bipolar II disorder have been conducted, consideration of maintenance treatment for this form of the illness is also strongly warranted [II]. The medications with the best empirical evidence to support their use in maintenance treatment include lithium [I] and valproate [I]; possible alternatives include lamotrigine [II] or carbamazepine or oxcarbazepine [II]. If one of these medications was used to achieve remission from the most recent depressive or manic episode, it generally should be continued [I]. Maintenance sessions of electroconvulsive therapy may also be considered for patients whose acute episode responded to electroconvulsive therapy [II].

For patients treated with an antipsychotic medication during the preceding acute episode, the need for ongoing antipsychotic treatment should be reassessed upon entering maintenance treatment [I]; antipsychotics should be discontinued unless they are required for control of persistent psychosis [I] or prophylaxis against recurrence [III]. While maintenance therapy with atypical antipsychotics may be considered [III], there is as yet no definitive evidence that their efficacy in maintenance treatment is comparable to that of agents such as lithium or valproate.

During maintenance treatment, patients with bipolar disorder are likely to benefit from a concomitant psychosocial intervention—including psychotherapy—that addresses illness management (i.e., adherence, lifestyle changes, and early detection of prodromal symptoms) and interpersonal difficulties [II].

Group psychotherapy may also help patients address such issues as adherence to a treatment plan, adaptation to a chronic illness, regulation of self-esteem, and management of marital and other psychosocial issues [II]. Support groups provide useful information about bipolar disorder and its treatment [I].

Patients who continue to experience subthreshold symptoms or breakthrough mood episodes may require the addition of another maintenance medication [II], an atypical antipsychotic [III], or an antidepressant [III]. There are currently insufficient data to support one combination over another. Maintenance sessions of electroconvulsive therapy may also be considered for patients whose acute episode responded to electroconvulsive therapy [II].

Refer to the original guideline document for a discussion of special clinical features influencing the treatment plan.

Definitions:

Grades of Recommendations:

- I. Recommended with substantial clinical confidence.
- II. Recommended with moderate clinical confidence.
- III. May be recommended on the basis of individual circumstances.

CLINICAL ALGORITHM(S)

None provided

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EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on the best available data and clinical consensus with regard to a particular clinical decision. The summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made (see the "Major Recommendations" field). In addition, the following coding system is used to indicate the nature of the supporting evidence in the references:

- [A] Randomized clinical trial
- [B] Clinical trial
- [C] Cohort or longitudinal study
- [D] Case-control study
- [E] Review of secondary analysis

[F] Review

[G] Other

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IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1994 Dec (revised 2002 Apr; reviewed 2005 Nov)

GUIDELINE DEVELOPER(S)

American Psychiatric Association - Medical Specialty Society

SOURCE(S) OF FUNDING

American Psychiatric Association (APA)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities many contributors have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. The guideline has been extensively reviewed by members of American Psychiatric Association (APA) as well as by representatives from related fields. Contributors and reviewers have all been asked to base their recommendations on an objective evaluation of the available evidence. Any contributor or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work has been asked to notify the APA Office of Research. This potential bias is then discussed with the work group chair and the chair of the Steering Committee on Practice Guidelines. Further action depends on the assessment of the potential bias.

GUIDELINE STATUS

According to the guideline developer, this guideline is still considered to be current as of November 2005. A Guideline Watch, which summarizes significant developments in practice since the publication of the original guideline, was published in November 2005 and is available from the [American Psychiatric Association Web site](#) (see also the "Availability of Companion Documents" field below).

GUIDELINE AVAILABILITY

Electronic copies: Available from the [American Psychiatric Association Web site](#).

Print copies: Available from the American Psychiatric Press, Inc (APPI), 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901; (703) 907-7322; (800) 368-5777; Fax (703) 907-1091.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- American Psychiatric Association practice guideline development process. In: practice guidelines for the treatment of psychiatric disorders: compendium 2000. Washington (DC): American Psychiatric Press, Inc (APPI), 2000.
- Hirschfeld RMA. Guideline watch: practice guideline for the treatment of patients with bipolar disorder, 2nd edition. Arlington (VA): American Psychiatric Association; 2005 Nov. 9 p. Electronic copies available in Portable Document Format (PDF) from the [American Psychiatric Association Web site](#).

Print copies: Available from the American Psychiatric Press, Inc (APPI), 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901; (703) 907-7322; (800) 368-5777; Fax (703) 907-1091.

Additionally, a continuing medical education (CME) course is available online at the [American Psychiatric Association Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 1, 1998. The information was verified by the guideline developer on January 11, 1999. This summary was updated by ECRI on April 17, 2002. The information was verified by the guideline developer on July 24, 2002. This summary was updated by ECRI on April 21, 2005 following the release of a public health advisory from the U.S. Food and Drug Administration (FDA) regarding Trileptal (oxcarbazepine). This summary was updated by ECRI on August 15, 2005, following the U.S. Food and Drug Administration advisory on antidepressant medications. This summary was updated by ECRI on October 3, 2005, following the U.S. Food and Drug Administration advisory on Paxil (paroxetine). This summary was updated by ECRI on December 12, 2005, following the U.S. Food and Drug Administration advisory on Paroxetine HCL - Paxil and generic paroxetine. This summary was updated by ECRI on January 18, 2006, following the U.S. Food and Drug Administration advisory on Clozaril (clozapine). This summary was updated by ECRI on May 31, 2006 following the U.S. Food and Drug Administration advisory on Paxil (paroxetine hydrochloride). This summary was updated by ECRI on November 15, 2006, following the FDA advisory on Lamictal (lamotrigine). This summary was updated by ECRI on November 21, 2006, following the FDA advisory on Effexor (venlafaxine HCl).

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DISCLAIMER

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