Special review article

Treatment guidelines for bipolar disorder: A critical review

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Abstract

Introduction: The development of treatment guidelines emerged as an important element so as to standardize treatment and to provide clinicians with algorithms, which would be able to carry research findings to the everyday clinical practice.

Material and method: The MEDLINE was searched with the combination of each one of the key words ‘mania’, ‘manic’, ‘bipolar’, ‘manic-depression’, ‘manic-depressive’ with ‘treatment guidelines’.

Results: The search was updated until March 1st, 2004 and returned 224 articles. Twenty-seven papers concerning the publication of treatment algorithms were traced.

Discussion: Despite supposedly being evidence-based, guidelines for the treatment of bipolar disorder vary significantly across committees or working groups. Overall, however, at the first stage of the mania/hypomania algorithm, monotherapy with lithium, divalproex sodium or olanzapine is generally recommended. At latter stages combination therapy is strongly recommended. It is clearly stated that in bipolar depression antidepressants should be used only in combination with antimanic agents in order to avoid switching of phases. During the maintenance phase all patients should receive antimanic agents, while some may need the addition of antidepressants. The most recent guidelines emphasize the use of atypical antipsychotics for mania and lamotrigine for depression. The main problem with guidelines is that they are rapidly outdated and that the evidence base relies mainly on registration monotherapy trials that hardly reflect treatment in routine clinical conditions.

Conclusion: Treatment guidelines may be useful to avoid non-evidence-based treatment decisions, but they are quickly out-of-date and may not fully apply to the clinical setting. The more recent guidelines point the value of atypical antipsychotics, lithium, and valproate in the treatment of mania; the role of lithium, lamotrigine, and olanzapine as options for maintenance therapy; and the scarcity of options for the treatment of bipolar depression. Psychoeducation is also supported by most guidelines as an adjunctive treatment.

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Keywords: Anticonvulsants; Antidepressants; Antipsychotics; Bipolar disorder; Evidence-based guidelines; Lithium; Mania; Mood stabilizers; Treatment

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1. Introduction

The development of treatment guidelines emerged as an important element so as to standardize treatment and to provide clinicians with algorithms, which would be able to carry research findings to the everyday clinical practice, by organizing information from diverse sources into an easily accessible format.

The aim of the current study is to review contemporary available treatment guidelines for bipolar disorder. Although several issues are relevant (adolescence, old age, pregnancy, comorbid conditions) this article focuses on the treatment guidelines concerning otherwise physically healthy and physiologically stable adults suffering from bipolar disorders.

2. Material and method

The MEDLINE was searched with the combination of each one of the key words ‘mania’, ‘manic’, ‘bipolar’, ‘manic-depression’, ‘manic-depressive’ with ‘treatment guidelines’ and ‘treatment algorithms’. The search returned 224 articles. The search was updated until March 1st, 2004. Finally the review process based on the titles and abstracts selected 84 of them for further study. Among them there were 23 papers concerning structured treatment algorithms proposed by official panels (1997; AACAP, 1997; Allen et al., 2001; American Psychiatric Association, 1994, 1995, 2002; Barreira et al., 1999; Bauer et al., 1999; Frances et al., 1996; Gilbert et al., 1998; Goodwin, 2003; Grunze et al., 2002; Grunze et al., 2003; Licht et al., 2003; McClellan and Werry, 1997; Montgomery, 2001; Rush et al., 1999, 2003; Sachs et al., 2000; Suppes et al., 1995, 2001, 2002, 2003). Another three papers on treatment guidelines (Goodwin et al., 1997; Jobson, 1997; Kusumakar et al., 1997) were traced by scanning the references list of review papers (Dennehy, 2000; Goldberg, 2000). One last paper published in July 2004 (Grunze et al., 2004) was brought by one of the authors (E.V.) who participated in that paper’s task force, thus raising the total number of guidelines reviewed here to 27. The guidelines are presented and discussed in the results section according to the chronological order the specific organization or panel started its effort to develop algorithms. The most important sources of guidelines are shown in Table 1.

3. Results

American Psychiatric Association treatment guidelines: The first detailed operational treatment guidelines concerning bipolar disorder published, were those of the American Psychiatric Association (American Psychiatric Association, 1994, 1995, 2002). Their development was based on expert opinion and reviewers which evaluated all available evidence. The first version was published in 1994. In that version, five types of medication were identified: Mood

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Major sources of guidelines development (in alphabetical order)</th>
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<tr>
<td>1.</td>
<td>American Psychiatric Association (APA)</td>
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<tr>
<td>2.</td>
<td>British Association for Psychopharmacology</td>
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<tr>
<td>3.</td>
<td>Canadian Network for Mood and Anxiety group</td>
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<tr>
<td>4.</td>
<td>Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark</td>
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<td>5.</td>
<td>Department of Veterans Affairs</td>
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<td>6.</td>
<td>ECNP Consensus Meeting March 2000 Nice</td>
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<td>7.</td>
<td>Expert Consensus Guideline Series</td>
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<td>9.</td>
<td>Texas Medication Algorithm Project</td>
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<td>10.</td>
<td>The Expert Consensus Guidelines for treating depression in bipolar disorder</td>
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<td>11.</td>
<td>The Expert Consensus Panel for Bipolar Disorder</td>
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<tr>
<td>12.</td>
<td>World Federation of Societies of Biological Psychiatry (WFSBP)</td>
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</tbody>
</table>
stabilizers (lithium, valproate, and carbamazepine), antimanic agents, antidepressant agents, adjunctive medication, and new or atypical medications. Lithium was considered the first choice in all phases of bipolar illness and superior to neuroleptics during the acute manic phase. Valproate and carbamazepine were considered as a second choice of treatment, and rather less effective than lithium. Benzodiazepines and neuroleptics were considered effective in the rapid control of agitation during the acute mania phase, but lithium was considered more effective concerning the normalization of mood. Antidepressants although effective in the treatment of bipolar depression are considered to worsen the overall course of bipolar disorder. ECT is reserved as the last resort, and the possibility to induce mania is stressed.

These guidelines were revised in 2002. The work group classified the guidelines into three categories reflecting the support from clinical data: I: Recommended with substantial clinical confidence; II: Recommended with moderate clinical confidence; and III: May be recommended on the basis of individual circumstances.

Mania/hypomania: The guidelines recommend the use of lithium plus an antipsychotic or valproate plus an antipsychotic as the first line of treatment (I). It is suggested that for less severely ill patients monotherapy with lithium, valproate, or an antipsychotic such as olanzapine may be sufficient (I). For mixed episodes, valproate may be recommended over lithium (II). Also atypical antipsychotics are preferred over typical ones (I), and most of the evidence support the use of olanzapine or risperidone (II). The second line of medication treatment includes the combination of two first line medications (I), adding carbamazepine or oxcarbazepine (II) or adding an antipsychotic (I). ECT should also be considered (I). When psychotic features are present, the use of an antipsychotic is necessary (I). Rapid cycling: Identify and treat medical conditions, drug or alcohol abuse (I), or various medication that may contribute to cycling (II). Use lithium or valproate and maybe lamotrigine (I). Combinations of medications are often necessary (II). Maintenance phase: Use lithium (I) and valproate (I) with possible alternatives being lamotrigine, carbamazepine or oxcarbazepine (II). Generally the agent that was successfully used for the treatment of the acute phase should be kept also during the maintenance phase (I). ECT maintenance sessions should also be considered (II). Antipsychotics should be discontinued unless they are required for control of persistent psychotic symptoms (I). Non-pharmacological treatments: Interpersonal and cognitive-behavioral psychotherapy as well as psychodynamic psychotherapy may be used in addition to pharmacotherapy (II), although empirical studies are inconclusive. During the maintenance phase, it is suggested that patients are likely to benefit from the application of a concomitant psychosocial intervention (II). Psychoeducational approaches may be more useful. Comments: These guidelines largely code generally accepted treatment without any radical suggestions. There is a clear suggestion that psychosocial therapies should be used only in combination with pharmacotherapy. Atypical antipsychotics are considered an adjunct treatment option. The work group also clearly states that higher doses of lithium so as to keep serum levels at 0.8–1.0 meq/l may be more effective during the maintenance phase.

The international psychopharmacology algorithm project for Bipolar Disorder (Suppes et al., 1995) was based largely on expert consensus. Lithium is considered to be the drug of choice for a first, second or third episode of mania. If there has been poor response or intolerance to lithium, or in cases of rapid cycling or mixed mania which respond poorly to lithium, the work group suggested first the use of valproate (as more supported by data) and afterwards carbamazepine. The addition of neuroleptics and/or benzodiazepines may be warranted. Before determining that response is inadequate the work group specifies a trial of at least two to three weeks, with lithium serum levels at least 0.8 meq/l or levels of carbamazepine or valproate corresponding to their established levels for the treatment of epilepsy. ECT is
suggested for refractory patients. The work group did not reach a consensus concerning the treatment of bipolar depression.

The 1st International Psychopharmacology Algorithm meeting produced therapeutic algorithms generally similar to the APA guidelines (Goodwin et al., 1997; Jobson, 1997). American Academy of Child and Adolescence Psychiatry: Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder (1997; McClellan and Werry, 1997): These guidelines concern the treatment of children and adolescents and thus are outside the focus of the current review.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) (Kusumakar et al., 1997). Mania/hypomania/mixed: The first choice of treatment for classic mania is lithium or divalproex. For more severe cases ECT is recommended. For psychotic or agitated patients it is recommended to use an antipsychotic or a benzodiazepine. Refractory patients should be treated with combinations of mood stabilizers. For mixed episodes divalproex or carbamazepine is recommended as the first choice. Bipolar depression: Treatment with a mood stabilizer; ECT is recommended for suicidal or patients with psychotic features. For refractory patients combinations of mood stabilizers with antidepressants are recommended along with ECT. Maintenance treatment: Treatment with mood stabilizer at optimal levels, with simultaneous discontinuation of all other agents once the patient is asymptomatic. Maintain treatment for 6–12 months after a single episode. For recurrent patients or for patients with family history maintenance treatment should be kept for life long. Non-pharmacological treatments: Cognitive-behavioural and interpersonal psychotherapy as adjunctive therapy in bipolar depression. Comments: These guidelines are generally in accord with the 1994 APA guidelines.

The Expert Consensus Guidelines for treating depression in bipolar disorder (1997; Frances et al., 1996, 1998). Mania: For patients with classic, euphoric mania, lithium and valproate are recommended. Valproate is recommended as the treatment of choice for mixed episodes, dysphoric mania, and mania in rapid cycling patients. Carbamazepine is considered a first line alternative for mixed episodes and for rapid cycling while lithium is also a first line alternative for mixed episodes. Adjunctive antipsychotics and/or benzodiazepines may be necessary, particularly if the patient has psychotic symptoms, agitation, or insomnia. The second line of treatment includes combinations of first line medications, ECT and atypical antipsychotics. Bipolar depression: The first line treatment for severe non-psychotic bipolar depression is the combination of a mood stabilizer plus an antidepressant. For milder episodes monotherapy with a mood stabilizer may be sufficient. For psychotic cases the first choice is ECT or the combination of an antidepressant, a mood stabilizer and an antipsychotic. SSRIs and bupropion are considered the antidepressants of choice and should be tapered faster than in unipolar depression. For refractory patients, add lithium or an anticonvulsant and use augmentation strategies or ECT. Continuation (2–6 months): Optimize the dose of the mood stabilizer. Other medications (antidepressants, antipsychotics, benzodiazepine) should be gradually tapered. Maintenance phase: Long-term or lifetime prophylaxis with a mood stabilizer is recommended. Non-pharmacological treatments: The authors also provide a detailed guide for psychotherapeutic and rehabilitation programs. Comments: These guidelines are in accord with the 1994 APA guidelines.

The clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs (Bauer et al., 1999). Mania/hypomania/mixed: The first choice is a mood stabilizer (lithium, valproate, carbamazepine and ECT). Valproate may be less effective than lithium in acute mania but more effective in mixed episodes. The patient should be maintained for 3 weeks on a therapeutic serum level (0.5–1.5 mmol/l for lithium, 45–125 μg/ml for valproate, 4–15 μg/ml for carbamazepine). ECT is the choice for refractory patients. Bipolar depression: Lithium is the first choice. The second step is to optimize the dosage and to add a second mood stabilizer to lithium and wait for another 6 weeks. ECT is another option, and the authors indirectly suggest that it should be considered before antidepressant medication. Antidepressants of all classes are considered a second line of choice. If the patient responds to antidepressant treatment, the agent should be tapered and discontinued within 6–12 weeks, although a subgroup of patients may require antidepressant treatment over extended periods of time.
For refractory patients the authors recommend augmentative strategies, combinations of antidepressants, ECT and alternative therapies like sleep deprivation or light therapy. Rapid cycling: Identify and treat conditions that may induce rapid cycling. Lithium is the first choice and other mood stabilizers are the second choice. Combination of mood stabilizers is the next step. Psychotic features: If psychotic features are present, a high or medium potency conventional or an atypical antipsychotic should be added, and should be discontinued 2–6 months after the resolution of psychotic symptoms. Comments: In essence, these guidelines are similar to the early (1994) APA guidelines.

The Texas Medication Algorithm Project (TMAP) for the treatment of bipolar disorder (Gilbert et al., 1998; Rush et al., 1999, 2003; Suppes et al., 2001, 2002, 2003). These guidelines were started developing in 1995, the first publication came in 1999 and their most recent version in 2002. Mania/hypomania: First stage: monotherapy with lithium, divalproex or olanzapine. Divalproex is recommended for any presentation of mania/hypomania, lithium is not recommended for dysphoric mania. In case of partial response, add a second agent rather than replacing the existing one. Second stage: combination therapy (choose among lithium, divalproex, oxcarbazepine, olanzapine, and risperidone). Third stage: try a different combination. Fourth stage: use directly an atypical antipsychotic in combination with lithium divalproex or oxcarbazepine. For patients with psychotic features it is recommended to proceed directly to this stage after stage 1. Fifth stage: proceed to triple therapy with the combination of lithium, an anticonvulsant (divalproex or oxcarbazepine) and an atypical antipsychotic (olanzapine, risperidone, quetiapine, or ziprasidone). Sixth stage: ECT or clozapine. Seventh stage: double antipsychotic therapy (conventional neuroleptics included), topiramate, lamotrigine, or other agents in various combinations according to the clinician’s opinion. Bipolar depression: First stage: optimization of mood stabilizing medication as described in the mania/hypomania algorithm. If the patient suffers also from major depression that warrants treatment, the clinician should proceed to stage 2, and add an SSRI (fluoxetine, paroxetine, sertraline fluvoxamine, and citalopram), buproprion extended release, or lamotrigine to existing medications. Third stage: add lithium, another antidepressant (venlafaxine or nefazodone) or a second one from stage 2 agents. At stage 4, use a combination of antidepressants from different classes, and choose from SSRIs, buproprion SR, lamotrigine, venlafaxine, and nefazodone. At the 5th stage, the clinician is prompted to change antidepressant medication to a monoamine oxidase inhibitor (MAOI) or to add an atypical antipsychotic. At the 6th stage, use ECT and ‘exploratory’ treatments (inositol, stimulants, dopamine agonists, hormones, conventional antipsychotics, tricyclic antidepressants—TCAs, omega-3 fatty acids, and acupuncture). Continuation phase: The treatment should be continued for at least 3 months at the dose effective during the acute phase. Maintenance phase: All patients should receive antimanic agents, while some will need the addition of antidepressants, at the lowest possible dose. Patients with 2 manic episodes or 1 which was severe or those with a positive family history of affective disorder will need a lifetime treatment. For the rest of patients gradually discontinue treatment 6 months in full remission. Comments: This group considers mania and antimanic medication as the core of bipolar disorder and its treatment, putting depression at a somewhat lower level, which is against empirical data. In addition, several therapies like ECT or TCAs, with proven efficacy are included only at the later stages, because of potential adverse effects or consumers’ opinion, however, this strategy puts them at the same level with therapies without any scientific support, like acupuncture. Finally the testing of the algorithms (but not of the final version (Suppes et al., 2002)) did not produce impressive results (Suppes et al., 2003).

The Expert Consensus Guideline Series Medication Treatment of Bipolar Disorder (Sachs et al., 2000): Mania: 1st step: For euphoric mania or hypomania the first choice is lithium or divalproex, while divalproex is preferred for dysphoric or mixed mania and if psychotic features are present. For the latter case, the addition of antipsychotics (olanzapine and risperidone) is recommended. Conventional antipsychotics are considered only when psychotic features are present. 2nd step: switching in case of lack of response or add another mood stabilizer (of those recommended in the 1st step) in case of partial response after 2–3 weeks. 3rd step: addition of carbamazepine or clozapine or ECT. 4th step: use various agents as topiramate, nimodipine, omega-3-
fatty acids, tiagabine, etc. **Bipolar depression**: 1st step: For milder episodes start with a mood stabilizer (Lithium or Valproex) alone. In severer ones add an antidepressant (SSRI or SNRI) and if antipsychotic features are present add an antipsychotic (Olanzapine or risperidone). ECT may be a first line option. The use of antipsychotics and antipsychotics should last from 1.5 to 5–6 months. 2nd step: use combinations of one or more mood stabilizers, antidepressants, and antipsychotics and switching to different agents. ECT and clozapine are valid alternatives. Other approaches include light therapy, augmentation strategies, stimulants, omega-3-fatty acids, sleep deprivation etc. **Rapid cycling**: Monotherapy with divalproex, lithium, carbamazepine, or lamotrigine; combinations and atypical antipsychotics for refractory patients. Avoid antidepressants or use non-SSRIs. **Maintenance treatment**: The treatment proved effective during the acute phase is recommended, with the exception of those patients suffering mainly from depressive episodes and treated with divalproex monotherapy. For those patient combination therapy with lithium plus divalprox is recommended. Antipsychotics should be discontinued, but for some patients in need for continuous antipsychotic medication, the therapist may choose between olanzapine, risperidone, and, alternatively, quetiapine. In case of a breakthrough manic episode, increase the dose of the stabilizer already applied, add a second one, then add adjunctive therapy and a third mood stabilizer. If there is a depressive breakthrough episode, again optimize the dosage of medication already applied, add a second mood stabilizer (divalproex or lithium) or lamotrigine or an antidepressant. **Comments**: This algorithm is too much detailed (covers 30 pages) and structured step by step; it reflects an overanalysis of expert opinion but it does not seem to rely heavily either on hard data or clinical experience.

**The ECNP Consensus Meeting Guidelines for Investigating Efficacy in Bipolar Disorder 2000** (Montgomery, 2001). This work group did not directly provide any detailed treatment guidelines. The general outline of the treatment plan suggested by this work group is largely in accord with the APA 1994 guidelines.

**The World Federation of Societies of Biological Psychiatry Guidelines for the Biological Treatment of Bipolar disorders**. This work group published guidelines for bipolar depression in 2002 (Grunze et al., 2002), mania in 2003 (Grunze et al., 2003), and maintenance treatment in 2004 (Grunze et al., 2004). **Mania**: First line: for acute euphoric mania lithium, valproate, olanzapine, risperidone, and carbamazepine; for mixed states of dysphoric mania valproate, olanzapine, risperidone, and carbamazepine, but not lithium. Typical antipsychotics should be avoided, but they are the first line of choice for severe episodes of mania and psychotic mania. In hypomanic episodes, use low doses of lithium or valproate or the short-term use of valproate or an atypical antipsychotic. Second line: use of combinations of lithium and/or and anticonvulsant plus an atypical antipsychotic or ECT. **Bipolar depression**: First line: use lithium, or a combination of antidepressants and mood stabilizers. Second line: use various combinations of first line agents, augmentation strategies and ECT. **Maintenance phase**: After a depressive episode, use a combination of antidepressants (SSRIs) and mood stabilizers (lithium, lamotrigine, valproate, or carbamazepine). After a manic episode, use lithium, an anticonvulsant or an antipsychotic. In case first line treatment fails, then the therapist should use combinations of first choice agents. **Comments**: These guidelines seem to be the most balanced to date. They are more advanced in comparison to the 1994 APA-like guidelines but at the same time they avoid going too far in recommending novel strategies. They favor the use of atypical antipsychotics and antidepressants, however with appropriate caution.

**The Expert Consensus Guideline Series Treatment of Behavioral Emergencies** (Allen et al., 2001). Their first line for acute mania is the oral or parenteral administration of the combination of a high potency conventional antipsychotic or an atypical antipsychotic (olanzapine or risperidone) plus a benzodiazepine. Antipsychotic or benzodiazepine monotherapy may be an alternative.

**Guidelines from the Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark** (Licht et al., 2003). **Mania/mixed**: If the patient is not on prophylactic treatment and for severely agitated patients, use an antipsychotic as a temporary supplement to treatment with lithium or an antiepileptic drug. Treatment with lithium or an antiepileptic may be sufficient even in cases of psychotic mania. For mixed mania,
valproate or olanzapine is recommended. If the patient was already on prophylactic treatment, then the prophylactic agent already applied should be raised, and the addition of an atypical antipsychotic or of a second prophylactic agent should be considered. Antidepressant drugs should be discontinued. Refractory patients should be treated with ECT. Bipolar depression: If the patient does not receive any prophylaxis and an depressive episode emerges, lithium or lamotrigine monotherapy is recommended for milder cases. If an antidepressant is used, concomitant therapy with a prophylactic agent should accompany the use of the antidepressant. In case the patient is already on lithium prophylaxis, the first step should be to optimize lithium dosage and then to add lamotrigine or an antidepressant (SSRI). If the patient already receives prophylactic treatment other than lithium, then lithium, lamotrigine, or an antidepressant should be added. In case of the presence of psychotic features, an antipsychotic (preferably an atypical) should be initiated. After the resolution of symptoms, antidepressants should be discontinued earlier than recommended for unipolar depression. ECT should be considered for refractory cases. Long-term treatment: Prophylactic drug treatment if at least 2 episodes occur within a period of 5 years although some patients may need prophylaxis after only one episode, judging on its severity. Duration of prophylaxis may range from 5 to 10 years. Lithium should be the first choice. Comments: The Danish guidelines are restricted to fundamental issues; they were developed with the Expert Opinion way.

**British Association for Psychopharmacology:** Evidence-based guidelines for treating bipolar disorder (Goodwin, 2003). Mania/mixed: For severe manic or mixed episodes use antipsychotics or valproate; for less severe episodes lithium or carbamazepine. The next step includes combination treatment (lithium or valproate plus an antipsychotic). Also consider clozapine and ECT. Antipsychotics and especially atypical ones should be used to treat psychotic features. Bipolar depression: Combination with an antidepressant (SSRIs) and an anti-manic agent (lithium, valproate, or an antipsychotic). Antidepressant monotherapy is not recommended. For less

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**Table 2**

Guidelines for the treatment of acute mania

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<thead>
<tr>
<th>1st choice</th>
<th>2nd step</th>
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<tr>
<td><strong>American Psychiatric Association, 1994</strong></td>
<td>Vp, Cbz</td>
</tr>
<tr>
<td><strong>American Psychiatric Association, 2002</strong></td>
<td>APs only for the rapid control of agitation</td>
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<tr>
<td>Texas Medication Algorithm Project 2002</td>
<td>ECT</td>
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<tr>
<td>British Association of Pharmacology 2003</td>
<td>ECT</td>
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<tr>
<td>World Federation of Societies of Biological Psychiatry 2003</td>
<td>Combos of MS+aAPs</td>
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**Table 3**

Guidelines for the treatment of acute bipolar depression

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<th>1st choice</th>
<th>2nd step</th>
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<tr>
<td><strong>American Psychiatric Association, 1994</strong></td>
<td>Li or La or Li+AD</td>
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<tr>
<td><strong>American Psychiatric Association, 2002</strong></td>
<td>ECT</td>
</tr>
<tr>
<td>Texas Medication Algorithm Project 2002</td>
<td>Li, Vp, Olz monotherapy or (Li, Vp, Olz)+(SSRI or La)</td>
</tr>
<tr>
<td>British Association of Pharmacology 2003</td>
<td>Severe: SSRIs+AM</td>
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<tr>
<td>World Federation of Societies of Biological Psychiatry 2003</td>
<td>(Li, Vp, AP)</td>
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severe episodes, monotherapy with lithium, lamotrigine, or valproate. For refractory patients use TCAs, augmentation strategies, and ECT. Antidepressants should be tapered shortly after the resolution of symptoms, after as little as 12 weeks. **Long-term treatment:** Lithium is the first choice. The second line consists of valproate, olanzapine, carbamazepine, and maybe oxcarbazepine and lamotrigine. Refractory patients may be treated with combinations of medications, clozapine or maintenance ECT.

4. Discussion

Bipolar illness has a complex clinical picture and an even more complex treatment. There are more than one traditional clinical approach to treatment with a traditional difference between academic authorities in Europe (in favor of the use of antipsychotics and antidepressants) and the US (in favor of so-called mood stabilizers).

The various treatment guidelines generally seem to have a common starting point, best described by the 1994 APA guidelines (American Psychiatric Association, 1994). But by passing the years and after revisions, today many guidelines deviate from this starting point. The guidelines that seem to deviate more than the others are the most recent Texas algorithms (Suppes et al., 2002; Tables 2–4). The most balanced seem to be those of the WFSBP (Grunze et al., 2002, 2003) which allow the use of multiple approaches with caution. The trend seems to be the gradual acceptance of the use of atypical antipsychotics as monotherapy and of antidepressants

<table>
<thead>
<tr>
<th>1st choice</th>
<th>2nd step</th>
<th>British Association of Pharmacology 2003</th>
<th>World Federation of Societies of Biological Psychiatry 2003</th>
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</thead>
<tbody>
<tr>
<td><strong>American Psychiatric Association, 1994</strong></td>
<td><strong>American Psychiatric Association, 2002</strong></td>
<td><strong>Texas Medication Algorithm Project 2002</strong></td>
<td><strong>After depression:</strong> AD+MS</td>
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<tr>
<td>Continue the treatment proved efficient during the acute phase</td>
<td>Li or Vp possibly Chz, La, Ocbz Continue the treatment</td>
<td>AM (Li, Vp, Olz) monotherapy or +AD (intermittent use) proved efficient during the acute phase</td>
<td>Li</td>
</tr>
<tr>
<td><strong>Predominantly mania:</strong> AM (Li, Vp, AP)</td>
<td><strong>Predominantly depression:</strong> (AD or La)+AM Clozapine Combinations ECT</td>
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for a limited period in combination with antimanic agents.

There are several key points of agreement between algorithms, but there are also several points of disagreement. Moreover, there are many issues that need further study, data are rare and insufficient and many questions remain unanswered (Table 5).

Since the publication of the most recent guidelines in 2003, several new developments emerged. Practically all atypical antipsychotics have proven to be efficacious in the treatment of acute mania (Vieta, 2003), olanzapine proved to be effective in the prevention of relapse after a manic episode (Tohen et al., in press) and, in combination with fluoxetine, in the treatment of bipolar depression (Tohen et al., 2003), quetiapine was better than placebo in bipolar depression as well (Calabrese et al., in press), and lamotrigine effectively prevented relapse in two long-term, controlled trials (Bowden et al., 2003; Calabrese et al., 2004). Psychoeducation, cognitive-behavioral therapy, and family intervention have been added successfully to treatment as usual to improve the outcome of the disease. Future guidelines should add these new data to provide meaningful and updated insight to the clinician. Many questions still remain unanswered, however, the main reason being that the evidence base for guidelines is still basically that which emerges from registration placebo-controlled trials, which enroll selected populations and tend to address monotherapy as opposed to combinations (Vieta and Carne, in press). Large, observational studies are also needed, and their results should be considered in future developments of current treatment guidelines.

References


