Treatment of bipolar disorder: a systematic review of available data and clinical perspectives

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Abstract

This paper is a systematic review of the available data concerning the treatment of bipolar disorder: a systematic Medline search concerning treatment guidelines and clinical trials. The search for treatment guidelines returned 583 articles and 913 papers for RCTs. The search was last performed on 1 March 2008. An additional search included repositories of clinical trials and previous systematic reviews in order to trace especially older trials. The literature suggests that lithium is useful during the acute manic and the maintenance phase. Both first- and second-generation antipsychotics are efficacious in the treatment of acute mania. Quetiapine and the olanzapine–fluoxetine combination are also effective for treating bipolar depression, while olanzapine, quetiapine and aripiprazole are effective during the maintenance phase. Anticonvulsants, particularly valproate and carbamazepine have antimanic properties, whereas lamotrigine may be preferably effective in the treatment of depression but not mania. Antidepressants should always be used in combination with an antimanic agent because they were reported to induce switching to mania or hypomania, mixed episodes, and rapid cycling when given as monotherapy. The best evidence-based psychosocial interventions for bipolar disorder are group- and family-focused psychoeducation. Electroconvulsive therapy is an option for refractory patients. Although a variety of treatment options for bipolar disorder is currently available, their effectiveness is far from satisfactory, especially against bipolar depression and maintenance. Combination therapy may improve treatment outcome but it also carries the burden of more side-effects. Further research as well as the development of better guidelines and algorithms for step-by-step rational treatment are necessary.

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Introduction

Hippocrates and Areteus were the first to describe manic-depressive illness but in modern time, bipolar disorder (BD) was first defined as an illness by Falret in 1851 (folie circulaire). BD type I and type II have a combined prevalence rate of up to 3.7% and both are disabling conditions. The first problem in the gathering of scientific proof concerning the treatment of affective disorders lies in the low reliability and validity of diagnosis. Judgement is often made retrospectively, and this is especially true for BD and carries the risk of memory distortions and biases. Another problem is that a specific and different treatment needs to be considered separately for manic, hypomanic, mixed and bipolar depression episodes, as well as for unipolar depression. Drugs proven effective for the acute phase of either pole should be tested in the maintenance phase (Vieta and Goikolea, 2005).

The comparator agent concerning bipolar illness is also an open question. The inclusion of a placebo group is important, because lack of such a group weakens the data and assay sensitivity (Vieta and Carne, 2005); such a design cannot provide sufficiently rigorous evidence since the underlying placebo response rate may be substantial and varies across and within studies. Active comparators, however, provide a better estimate of benefit-risk ratio. An ideal study should therefore include at least three groups: placebo, active comparator, and drug under investigation group simultaneously.

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The treatment of bipolar illness is complex and full of caveats for the clinician (Fountoulakis et al., 2005, 2007a,b, 2008a). The present study attempts to perform a systematic review of the available data on the treatment of bipolar illness in order to summarize the current status of our knowledge and practice concerning the treatment of BD and suggest future directions for research and development of guidance on the basis of real-world clinical needs.

**Material and Method**

Medline was searched in order to locate papers with treatment guidelines and randomized controlled trials (RCTs) concerning the agents frequently used in the treatment of bipolar illness. The search was last performed on 1 March 2008.

The following search strategies were followed:

1. In order to locate treatment guidelines, 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’.


3. A third strategy was applied for lithium, valproate and carbamazepine because it appeared that older trials (conducted during the 1970s) were missing from the previous search. Thus the name of the substance plus the word ‘placebo’ were used in the search.

The authors searched for placebo-controlled as well as for clinical trials with an active comparator with the compounds used as monotherapy. Papers concerning add-on therapy were also included in order to complete the picture. The data were graded on the basis of the POST method (Lehman and Steinwachs, 1998) as modified for use by the World Federation of Societies of Biological Psychiatry for the development of the WFSBP guidelines (Grunze et al., 2002, 2003, 2004).

Results of the literature search

The literature search returned 583 papers concerning guidelines. Among them there were 32 papers concerning structured treatment algorithms proposed by official panels (Anon, 1997; AACAP, 1997; Allen et al., 2001; APA, 1994, 1995, 2002; Barreira et al., 1999, Bauer et al., 1999; Dennehy, 2000; Frances et al., 1996; Gilbert et al., 1998; Goldberg, 2000; Goodwin et al., 1997; Goodwin, 2003; Grunze et al., 2002, 2003, 2004; Jobson, 1997; Kusumakar et al., 1997; Licht et al., 2003; McClellan and Werry, 1997; Montgomery, 2001; O’Dowd, 2006; Rush et al., 1999, 2003; Sachs et al., 2000; Suppes et al., 1995, 2001, 2002, 2003; Yatham et al., 2005, 2006). One additional source of guidelines was traced, the APA Watch which is an electronic source available online (Hirschfeld, 2005). The number of 583 papers originally traced, compared to the number of 224 articles traced with the same methodology on 1 March 2004, constitutes a 260% increase in the number of articles in 4 years and reflects the great interest of the psychiatric community in the field.

The Medline search for RCTs returned 913 papers. Most of them concerned opinion or review papers, open studies, complex combination or adjunctive therapy, many focusing on different agents and only a small minority of papers could be considered as RCTs proper for the agent under consideration.

**Lithium**

**Randomized placebo-controlled studies**

**Acute Mania**

There are two placebo-controlled studies (Bowden et al., 1994, 2005) suggesting that the percentage of acutely manic patients that responded (at least 50% reduction of symptoms) is around 49% for lithium vs. 25% for placebo. Two other studies comparing lithium to topiramate confirmed the efficacy of lithium (Kushner et al., 2006). Another study comparing lithium to aripiprazole suggests that although they were equal at endpoint, aripiprazole acted faster (Keck et al., 2007a).
Acute bipolar depression

A recent 8-wk comparison of lithium vs. quetiapine in acute bipolar depression was negative for lithium (Young et al., 2008).

Maintenance phase

Although there was an earlier study (Goodwin et al., 1969), the first real placebo-controlled study was a discontinuation one. It included 50 stabilized bipolar patients (Bastrup et al., 1970). Later, Prien studied 205 and 31 patients immediately after the resolution of the acute episode (Prien et al., 1973a). A similar study sample was used by Pokorny (Pokorny and Prien, 1974). Kane studied 22 bipolar II patients in remission for at least 6 months and randomly assigned them to lithium, imipramine, lithium + imipramine, or placebo. Lithium was found to help prevent relapse of any type among those with bipolar II disease. No effect or interaction of imipramine was found in either group (Kane et al., 1982). Several other small studies exist with samples of 15 (Melia, 1970), 18 (Fyro and Petterson, 1977), 53 (Fieve et al., 1976) and 24 patients (Cundall et al., 1972). Although all the above studies report positive results for lithium, the generally small size does not permit a formal analysis.

Although earlier maintenance placebo-controlled studies suggested lithium was effective for the prophylaxis against both mania and bipolar depression (Dunner et al., 1976; Glen et al., 1984; Prien, 1984; Prien et al., 1973a,b, 1984), later studies suggest that lithium is effective in the prevention of manic episodes but possibly not for depressive episodes (Bowden et al., 2000a, 2003; Calabrese et al., 2003a, 2006; Goodwin et al., 2004; Kane et al., 1982). According to meta-analysis, this supposed selectivity of lithium against mania could be a biased result caused by the discontinuation design of many studies, since discontinuation seems to predispose more to mania than depression (Burgess et al., 2001). The overall efficacy during the maintenance phase appears to be rather weak, since the average risk of relapse in the placebo group was 60% compared with 40% for lithium. Concerning manic episodes alone, the average risk of relapse in the placebo group was 24% compared with 14% for lithium. This difference was significant in contrast to the risk concerning depressive episodes which for the placebo group was 32% compared with 25% for lithium and was marginally non-significant (Geddes et al., 2004).

Studies with mixed and small samples (Fieve et al., 1976; Hullin et al., 1972; Klein et al., 1981; Prien et al., 1973b), small non-randomized case-control studies with placebo (Margo and McMahon, 1982; Persson, 1972), small crossover studies (Mander and Loudon, 1988) and discontinuation studies (Bastrup et al., 1970; Christodoulou and Lykouras, 1982; Cundall et al., 1972; Hullin et al., 1972; Kafantaris et al., 2004; Melia, 1970; Small et al., 1971) are all difficult to interpret. Discontinuation studies are more difficult to interpret for a variety of reasons including shorter duration of the study and a lithium-discontinuation-related refractoriness (in up to 15% of patients) (Post et al., 1992).

Conclusively, the literature is supportive concerning the efficacy of lithium against mania both during the acute phase and as a prophylactic agent, but possibly not against bipolar depression. However it seems that lithium is also effective against subsyndromal symptoms of both polarities during the maintenance phase (Frye et al., 2006) as well as for the treatment of concomitant substance abuse (Geller et al., 1998, 1992).

Randomized studies without a placebo arm

Acute mania

An earlier small study on 23 patients comparing lithium vs. chlorpromazine reported that lithium was superior against acute mania at week 3 but the difference was not significant (Platman, 1970). More recent studies suggest that lithium is as effective as olanzapine (Berk et al., 1999) but may be less effective in specific populations like those with mixed features. A recent, unpublished trial (F1D-GH-LOBV) as well as a published one (Niufan et al., 2008), suggest olanzapine is more effective than lithium but with more adverse effects. It is reported to be equivalent to lamotrigine (Ichim et al., 2000) and risperidone, chlorpromazine and haloperidol (Segal et al., 1998; Shopsin et al., 1975). Two studies suggest it is equivalent to carbamazepine (Okuma et al., 1990; Small et al., 1991) but another one suggests it is superior to it (Lerer et al., 1987), while a further study suggests it is superior to valproate (Freeman et al., 1992).

Acute bipolar depression

There are no comparative studies in acute bipolar depression apart from the previously mentioned quetiapine vs. lithium study, which had a placebo arm (Young et al., 2008).

Maintenance phase

One study reported that olanzapine was superior to lithium in the prophylaxis against manic and mixed...
episodes and with similar efficacy against depressive episodes (Tohen et al., 2005) while another one found them to be equivalent (Houston et al., 2005). Lithium appears to be as effective as valproate in the prophylaxis of rapid-cycling patients (Calabrese et al., 2005b) and paediatric patients (Findling et al., 2005). Several studies suggest it is not superior to carbamazepine although there is a trend for lithium to perform slightly but not significantly better (Coxhead et al., 1992; Denicoff et al., 1997; Greil and Kleinidest, 1999a,b; Greil et al., 1997; Kleinidest and Greil, 2002; Lusznat et al., 1988; Placidi et al., 1986; Simhandl et al., 1993; Small et al., 1991; Stoll et al., 1989; Watkins et al., 1987).

A post-hoc analysis suggests that using olanzapine early in the course of the disorder is possibly more beneficial than lithium during the maintenance phase (Ketter et al., 2006). Adding lithium to low doses but not to high doses of haloperidol increases efficacy against acute mania (Chou et al., 1999) while the combination with imipramine produced no advantage but also no switches to the opposite pole (Quitkin et al., 1981a,b). An interesting although with a problematically low-dose study contrasted lithium vs. placebo in patients receiving cognitive behaviour treatment and found no difference between lithium and placebo (Wilson et al., 1995). Another study reported that lithium was less effective than valproate when added on antidepressants for the prevention of bipolar depression (Gyulai et al., 2003).

Drawbacks of lithium therapy include its narrow therapeutic index (recommended plasma level 0.8–1.2 mmol/l), poor tolerability, especially at higher doses, and risk of ‘rebound mania’ on withdrawal (Goodwin, 1994). Common side-effects of lithium are tremor, polydipsia, polyuria, and in the long-term, hypothyroidism. However, in spite of these shortcomings, lithium still remains the gold standard of anti-bipolar treatment with the possibility of also possessing an antisuicidal effect (Baldessarini et al., 2006; Gonzalez-Pinto et al., 2006).

**Antipsychotics**

**Amisulpride**

There are no double-blind, placebo-controlled trials with amisulpride as monotherapy for the treatment in mania. There are only open-label studies (Carta et al., 2006; Vieta et al., 2005d) and one open-label randomized comparison of amisulpride with haloperidol as combination treatment with valproate (Vieta et al., 2006b). These studies support the use of amisulpride in acute mania, but in the absence of stronger evidence, this conclusion should be viewed with caution. Hyperprolactinaemia and extrapyramidal symptoms (EPS) are the most usual adverse effects with amisulpride.

**Aripiprazole**

**Randomized placebo-controlled studies**

**Acute mania**

There are six monotherapy, placebo-controlled studies. Two of them suggest that 15–30 mg aripiprazole treatment produces a 10–20% greater response than placebo against manic and mixed episodes (Keck et al., 2003a, 2007a; Sachs et al., 2006). The fourth unpublished study is negative (Garcia-Amador et al., 2006). Two recent studies compared aripiprazole with placebo and an active comparator, haloperidol (A. Young et al., unpublished observations), and lithium (Keck et al., 2007a).

Meta-analytical studies confirmed that aripiprazole is effective against acute mania (Suppes et al., 2008a). The effect of aripiprazole is considered to be specific and not attributed to sedation alone (Sachs et al., 2007a).

**Acute bipolar depression**

Two 8-wk placebo-controlled trials were negative at study endpoint (Thase et al., 2008).

**Maintenance phase**

Aripiprazole is reported to protect from manic relapses but there were no statistical differences in depressive relapses compared to placebo (Keck et al., 2006, 2007b).

**Randomized studies without a placebo arm**

In a 12-wk comparison to haloperidol, aripiprazole showed superior levels of response and tolerability to haloperidol in the treatment of an acute manic episode (Vieta et al., 2005a).

There is one placebo-controlled trial with aripiprazole as adjunctive treatment to mood stabilizers, which showed significantly better efficacy on the primary outcome for the combination vs. lithium or valproate alone (Vieta et al., in press b).

Akathisia and EPS are the adverse effects most often reported with aripiprazole.

**Asenapine**

There are no published trials on asenapine in BD, but a number of completed trials now exist. So far only
the results of two randomized, 3-wk double-blind, placebo-controlled trials (Ares 7501004 and Ares 7501005) on 960 adult bipolar I patients with moderate-to-severe mania have been announced. Patients received either asenapine (5–10 mg twice daily), olanzapine (5–20 mg once daily) or placebo, and at day 21 in both studies, both asenapine and olanzapine produced significant mean improvements in the Young Mania Rating Scale (YMRS) vs. placebo. Currently the results of a 9-wk trial of asenapine vs. olanzapine (Ares A7501006), a 12-wk and a 40-wk placebo-controlled study of the safety and efficacy of asenapine when added to lithium or valproate (NCT00145470 and NCT00145509) and a 40-wk extension study of asenapine vs. olanzapine (Ares 7501007) are expected to be announced.

Chlorpromazine

Chlorpromazine is the antipsychotic which launched the modern psychopharmacological era, and probably many of the agitated patients it was initially tried on, were suffering from acute mania. However, until the present, there is only one early, small, placebo-controlled study (Klein, 1967), plus three randomized comparative studies: vs. lithium, haloperidol, and pimozide (Cookson et al., 1981; Prien et al., 1972; Shopsin et al., 1975). The results from these studies suggest chlorpromazine is more efficacious in the treatment of acute mania compared to placebo and equivalent to lithium and the other antipsychotics.

The most frequent side-effects of chlorpromazine are EPS, tardive dyskinesia, postural hypotension and hepatotoxicity (Prien et al., 1972).

Clozapine

Clozapine is the prototype atypical antipsychotic but it is not as widely used and studied as the others, mainly due to its risks of agranulocytosis. To date there have been no double-blind, placebo-controlled clinical trials assessing clozapine in the treatment of acute mania or depression. There are a few, small-sample, open-label studies, suggesting that clozapine may be effective in the treatment of acute mania (Barbini et al., 1997; Calabrese et al., 1996; McElroy et al., 1991) and one randomized add-on study suggesting clozapine is superior to treatment as usual in the prevention of mania in refractory patients (Suppes et al., 1999).

Besides the potential risk for agranulocytosis and seizures, other potential side-effects of acute use of clozapine include clinically significant weight gain, the induction of a metabolic syndrome and sialorrhoea.

Haloperidol

Randomized placebo-controlled studies

For haloperidol there are studies only against acute mania. The results of the first placebo-controlled study of haloperidol vs. lithium, chlorpromazine and pimozide suggests that haloperidol is more efficacious in the treatment of acute mania compared to placebo and equivalent to lithium and chlorpromazine (Shopsin et al., 1975). More recent studies suggest that haloperidol (up to 8 mg/d) is superior to quetiapine (up to 800 mg/d) at week 3 but not at week 12 against acute mania (McIntyre et al., 2005) and that 2–12 mg/d haloperidol is equivalent to 1–6 mg/d risperidone (Smulevich et al., 2005) and to aripiprazole (A. Young et al., unpublished observations). High doses of haloperidol were superior to placebo and ziprasidone in another trial (Dunn et al., 2006; Vieta et al., in press a).

Randomized studies without a placebo arm

Comparative studies suggest haloperidol is equivalent to risperidone and lithium (Segal et al., 1998), and olanzapine (Tohen et al., 2003a). It has been reported that 25 mg/d is superior to 5 mg/d against acute mania but with more side-effects (Chou et al., 1999). In a 12-wk comparison to haloperidol, aripiprazole showed superior levels of response and tolerability to haloperidol in the treatment of an acute manic episode (Vieta et al., 2005a). Moreover, intramuscular (i.m.) haloperidol was equal in efficacy but faster acting compared to i.m. clonazepam in agitated mania (Chouinard et al., 1993). Valproate oral loading (20 mg/kg.d) was equivalent to 0.2 mg/kg.d haloperidol for the treatment of exited manic patients in a single-blind study (McElroy et al., 1996).

One study suggests that 10–15 mg/d haloperidol was less effective compared to 15–30 mg/d aripiprazole in the treatment of acute manic/mixed patients and less well tolerated (Vieta et al., 2005a) or equivalent to olanzapine (Tohen et al., 2003a). Small earlier comparison studies do not permit a valid interpretation (Brown et al., 1989). It has also been reported that haloperidol could decrease the time to switch into depression compared with atypical antipsychotics (Tohen et al., 2003a).

Add-on studies reported that adding haloperidol to lithium was similar to adding lorazepam (Lenox et al., 1992) or carbamazepine (Small et al., 1995). In another study, it was the low dose (5 mg/d) not the high dose (25 mg/d) which could be augmented by adding lithium but not lorazepam (Chou et al., 1999). Another study reported that haloperidol + valproate was more...
effective against acute mania than valproate + placebo (Muller-Oerlinghausen et al., 2000) and that haloperidol + valproate or lithium was also more effective than valproate or lithium + placebo and equivalent to risperidone + valproate or lithium (Garfinkel et al., 1980; Sachs et al., 2002).

Haloperidol adverse effects include EPS, tardive dyskinesia and hyperprolactinaemia.

Olanzapine

Randomized placebo-controlled studies

Acute mania

At 10 mg/d it has been reported that 48.6% of patients under olanzapine responded compared to 24.2% under placebo (Tohen et al., 1999). A dose of 5–20 mg/d produces a 65% response vs. 43% of placebo and 61% of patients achieve full remission vs. 36% under placebo (Tohen et al., 2000). In adolescents it produces a 44.8% response vs. 18.5% of placebo and 35.2% remission vs. 11.1% of placebo (Tohen et al., 2007). Intramuscular olanzapine is reported to be superior to benzodiazepines or placebo for controlling agitation in manic patients (Meehan et al., 2001).

Meta-analytical studies suggest that olanzapine is effective against dysphoric mania concerning both manic and depressive symptoms (Baker et al., 2003) and irrespective of factors like sex, age at onset, rapid cycling or psychotic features (Baldessarini et al., 2003a) or prior history of good or poor response to lithium or anticonvulsants (Baker et al., 2002). The overall response rate is superior to placebo (55% vs. 29.5%) (Chengappa et al., 2003).

Acute bipolar depression

There is one study which reported that the remission criteria were met by 24.5% of the placebo group, 32.8% of the olanzapine group, and 48.8% of the olanzapine–fluoxetine combination (OFC) group. Treatment-emergent mania did not differ among groups. Thus, olanzapine is more effective than placebo, and OFC is more effective than olanzapine and placebo in the treatment of bipolar I depression without increased risk of developing manic symptoms (Tohen et al., 2003c). However, the study sample was small concerning the OFC arm (n = 86) and there are some concerns on the effect treatment had on the ‘depressive core’ of symptoms, i.e. those symptoms representing the core concept of depression (e.g. depressed affect, anhedonia, etc.). In contrast, the patients manifested a significant improvement in symptoms ‘ peripheral’ to the definition of depression, e.g. insomnia, anxiety, loss of appetite, etc. (Bech, 2001; Lecrubier and Bech, 2007).

The meta-analysis suggests that OFC is superior to olanzapine alone, has improved many secondary indices (Shi et al., 2004) and shown a beneficial effect from day 7 (Dube et al., 2007).

Maintenance phase

One study suggests that after 48 wk the relapse rate was significantly lower in the olanzapine group (46.7%) than in the placebo group (80.1%) and this was true concerning manic, depressive and mixed episodes (Tohen et al., 2006).

Randomized studies without a placebo arm

Acute mania

One study suggested that olanzapine was superior to valproate against manic or mixed episodes (Tohen et al., 2002a) but another one suggests they are equivalent with valproate having a more favourable adverse-effects profile (Zajecka et al., 2002). The same conflict of results exists for lithium with one study suggesting it is similar but better tolerated than lithium (Berk et al., 1999), while an unpublished study (FID-GH-LOBV) as well as a published one, suggest olanzapine is more effective than lithium but also with more adverse effects (Niufan et al., 2008). Other studies report olanzapine as equivalent to risperidone (Perlis et al., 2006a) and haloperidol (Tohen et al., 2003a).

A post-hoc analysis suggests olanzapine is superior to valproate in rapid cycling and equivalent in classic manic patients (Suppes et al., 2005).

Acute bipolar depression

One study suggests that OFC is somewhat superior to lamotrigine although the response rates did not differ between groups (OFC: 68.8% vs. lamotrigine 59.7%). The time to response was significantly shorter for the OFC-treated patients (OFC 17 days vs. lamotrigine 23 days) and there were lesser ‘suicidal and self-injurious behaviour’ among OFC-treated patients (OFC 0.5% vs. lamotrigine 3.4%) (Brown et al., 2006).

Maintenance phase

Olanzapine was found to be superior to lithium in the prophylaxis against manic and mixed episodes and with similar efficacy against depressive episodes (Tohen et al., 2005). It is also reported to be similar concerning the prevention of manic episodes but did
slightly better than valproate concerning YMRS (Tohen et al., 2003b).

A post-hoc analysis suggests that using olanzapine early in the course of the disorder is possibly more beneficial than lithium during the maintenance phase (Ketter et al., 2006). Adding olanzapine to lithium or valproate improves outcome (Tohen et al., 2002b, 2004) and may reduce suicidality (Houston et al., 2006). Overall, there are strong data supporting the usefulness of olanzapine during all phases of BD (Rendell et al., 2003), although it may be particularly useful in patients with manic predominant polarity (Colom et al., 2006; Rosa et al., 2008). The most frequent adverse effects include dry mouth, weight gain, increased appetite and somnolence (Tohen et al., 2002a). Another problem with olanzapine is that it is believed to carry some risk of developing metabolic syndrome and diabetes mellitus.

**Perphenazine**

There is only one 6-month maintenance study with a placebo-controlled double-blind design of perphenazine + lithium, carbamazepine, or valproate or a mood stabilizer + placebo in patients just remitted from an acute manic episode. The results suggested that patients receiving perphenazine did not have a better course compared to those receiving placebo, but on the contrary they had a shorter time to depressive relapse, more drop-outs, and increased rates of dysphoria and depressive symptoms (Zarate and Tohen, 2004).

**Quetiapine**

**Randomized placebo-controlled studies**

**Acute mania**

Quetiapine up to 800 mg/d was superior to placebo with response criteria at day 21 being met by 53.3% of quetiapine-treated patients vs. 27.4% of placebo and also at day 84 (72.0% vs. 41.1%). However lithium was proven superior concerning the YMRS score which was the primary efficacy measure (Bowden et al., 2005). In another trial, haloperidol (up to 8 mg/d) was superior to quetiapine (up to 800 mg/d) at week 3 but not at week 12 (McIntyre et al., 2005). A pooled analysis confirmed efficacy and good tolerability. The adverse events included somnolence, dry mouth, weight gain and dizziness (Vieta et al., 2005b).

**Acute bipolar depression**

The use of 600 and 300 mg/d of quetiapine produced response rates of 58.2% and 57.6%, respectively, vs. 36.1% for placebo. Remission rates were 52.9% in the groups taking 600 and 300 mg/d quetiapine vs. 28.4% for placebo. Quetiapine significantly improved the Montgomery–Asberg Depression Rating Scale (MADRS) items corresponding to the core symptoms of depression. Treatment-emergent mania rates were low and similar for the quetiapine and placebo groups (3.2% vs. 3.9%, respectively) (Calabrese et al., 2005a; Thase et al., 2006). Similar results were obtained from a recent study which was simultaneously negative for lithium (Young et al., 2008) and another study which was negative for paroxetine (McElroy et al., 2008).

Post-hoc analysis suggests that the dose of 300 mg is not inferior to 600 mg in spite of a different effect size, and both are superior to placebo (Cookson et al., 2007) and improved secondary measures including quality-of-life indices (Endicott et al., 2007). It also suggests that quetiapine is effective against depression in rapid-cycling bipolar I or II patients (Vieta et al., 2007a).

**Maintenance phase**

There are no monotherapy trials published yet, but there are two positive, add-on, placebo-controlled trials (Suppes et al., 2008b; Vieta et al., 2007b).

**Randomized studies without a placebo arm**

**Acute mania**

Quetiapine is superior to valproate in adolescents with manic or mixed episodes (DelBello et al., 2006).

**Acute bipolar depression**

There are no studies of this kind against acute bipolar depression yet, although as mentioned previously two placebo-controlled trials had an active arm (lithium in one and paroxetine in the other) which were negative for the comparator (McElroy et al., 2008; Young et al., 2008).

**Maintenance phase**

There are no studies of this kind concerning the maintenance phase.

Adding quetiapine to valproate increases efficacy against acute mania in adolescents (DelBello et al., 2002) and adding it to lithium or valproate in adult manic patients again improves outcome (54.3% vs. 32.6% and 55.7% vs. 41.6%) (Sachs et al., 2004; Suppes et al., 2008b; Yatham et al., 2004). However, a more recent study does not support the above (Yatham et al., 2007). Two recent placebo-controlled add-on trials of quetiapine + mood stabilizer during maintenance...
treatment, suggest that quetiapine is superior to placebo in the prevention of manic and depressive recurrences in either manic, depressive, or mixed index episode over a period of 2 yr (Vieta et al., 2007b). These add-on studies appear to be the first to report prevention on both depression and mania regardless of the type of index episode.

The main adverse effects of quetiapine are persistent sedation and weight gain, although to a lesser extent than either clozapine or olanzapine.

**Risperidone**

*Randomized placebo-controlled studies*

**Acute mania**

Risperidone at doses of 1–6 mg/d manifest a remission rate of 42% vs. 13% of placebo (Gopal et al., 2005) and the improvement is evident from day 3 (Hirschfeld et al., 2004; Khanna et al., 2005). Risperidone (1–6 mg/d) is equivalent to 2–12 mg/d haloperidol (Smulevich et al., 2005). Some studies included patients with mixed states (Hirschfeld et al., 2004; Khanna et al., 2005; Smulevich et al., 2005).

The Indian study (Khanna et al., 2005) sparked a debate concerning the extent of the use of placebo in similar studies (Mudur, 2006; Patel, 2006).

**Acute bipolar depression**

No studies.

**Maintenance phase**

No studies.

*Randomized studies without a placebo arm*

**Acute mania**

Risperidone was reported to be equivalent to olanzapine (Perlis et al., 2006a), and to lithium and haloperidol (Segal et al., 1998).

**Acute bipolar depression**

No studies.

**Maintenance phase**

No studies.

**Ziprasidone**

*Randomized placebo-controlled studies*

**Acute mania**

In four studies published in two papers, 80–160 mg/d ziprasidone was reported to be rapidly (by day 2) effective against acute manic or mixed episodes (Keck et al., 2003b; Potkin et al., 2005). A third monotherapy, placebo-controlled trial (Vieta et al., in press a) also had a haloperidol arm and showed significant superiority over placebo but significantly lower efficacy vs. haloperidol (up to 30 mg/d) at the 3-wk and 12-wk endpoints [primary outcome, mania rating scale (MRS) improvement at week 3: ziprasidone, 11.6; haloperidol, 16.6; placebo, 6.6].

**Acute bipolar depression**

No studies.

**Maintenance phase**

No studies.

*Randomized studies without a placebo arm*

**Acute mania**

No studies.

**Acute bipolar depression**

No studies.

**Maintenance phase**

No studies.

An add-on, unpublished study of 80–120 mg/d ziprasidone vs. placebo on top of lithium was negative concerning the primary outcome which was the YMRS (Weisler et al., 2003).

Somnolence, akathisia and EPS, as well as a QTc prolongation are the main adverse effects of ziprasidone treatment (Potkin et al., 2005).
Anticonvulsants

Anticonvulsants appear to possess a broad spectrum of activity on BD, including mixed dysphoric and rapid-cycling forms. Lithium, by contrast, seems more specific to euphoric mania.

Valproate

Randomized placebo-controlled studies

Acute mania

The first study reported a robust 54% decrease in scores on the YMRS of patients under valproate vs. 5% of patients under placebo (Pope et al., 1991).

Subsequent studies report that valproate at doses leading to serum levels of 150 µg/ml produced a 48% response compared to 49% for lithium and 25% for placebo, with valproate being as effective in rapid-cycling manic patients as in other patients (Bowden et al., 1994).

At the dose leading to serum levels of 85–125 µg/ml, the improvement from baseline was significantly greater among patients under valproate compared with placebo by day 5. Responders were 48% vs. 34% with placebo (Bowden et al., 2006).

Earlier studies with very small study samples and a very different study design (ABA design) were also positive but also difficult to interpret (Emrich et al., 1980, 1981).

Acute bipolar depression

There are only two small studies (25 and 18 patients) suggesting that valproate is effective in reducing the symptoms of depression and anxiety in bipolar I patients during the acute depressed phase (Davis et al., 2005; Ghaemi et al., 2007).

Maintenance phase

There is one negative 12-month maintenance study which reported that the valproate group did not differ significantly from the placebo group in ‘time to any mood episode’. In this study, however, lithium also produced negative results, thus a possible explanation could be that the study sample was problematic. Valproate was superior concerning some of the secondary outcomes, e.g. less deterioration in depressive symptoms and Global Assessment Scale (GAS) scores (Bowden et al., 2000a).

Randomized studies without a placebo arm

Acute mania

An earlier study suggested 1500–3000 mg/d valproate was inferior to lithium at serum levels of 1.5 mmol/l but unlike the case with lithium, favourable response to valproate was associated with high pretreatment depression scores, suggesting that treatment with valproate alone may be particularly effective in manic patients with mixed affective states (Freeman et al., 1992).

A different result was reported by another study suggesting that valproate oral loading (20 mg/kg.d) may produce rapid onset of antimanic and anti-psychotic response comparable to that of haloperidol and with minimal side-effects in the initial treatment of acute psychotic mania in a subset of bipolar patients (McElroy et al., 1996).

Valproate loading is reported to be safe and well tolerated (Hirschfeld et al., 1999).

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Comparison of olanzapine (5–20 mg/d) with valproate (500–2500 mg/d in divided doses) for the treatment of patients hospitalized for acute bipolar manic or mixed episodes, suggested that 47.2% of olanzapine-treated patients had remission of mania symptoms vs. 34.1% of valproate-treated patients (Tohen et al., 2002a).

However, another study reported equal effectiveness between olanzapine and valproate with valproate having a more favourable adverse-effects profile (Zajecka et al., 2002).

The last study reported that valproate at serum levels of 80–120 µg/ml was equivalent to 400–600 mg/d quetiapine for the treatment of acute manic symptoms associated with adolescent BD, but quetiapine might act faster (DelBello et al., 2006).

Acute bipolar depression

No studies.

Maintenance phase

Maintenance studies suggest valproate is equivalent to lithium concerning any mood episode (Calabrese et al., 2005b), not superior to lithium as maintenance treatment in youths who were stabilized on a combination of lithium + valproate (Findling et al., 2005) and that the overall per-patient treatment costs are similar for olanzapine and valproate (Zhu et al., 2005).

One study reported that adding valproate to neuroleptics improves outcome (70% vs. 46%) (Muller-Oerlinghausen et al., 2000). Another study reported that valproate was superior to lithium or placebo when added on antidepressants for the prevention of bipolar depression (Gyulai et al., 2003).

There is concern whether valproate should be used in women at childbearing age, due to the high frequency of unplanned pregnancies in bipolar females, and the relatively high teratogenicity of the
compound. Other potential acute side-effects of valproate are weight gain and hair loss. Moreover, valproate has controversially been reported to induce polycystic ovarian syndrome.

**Carbamazepine**

**Randomized placebo-controlled studies**

**Acute mania**

An earlier study utilized withdrawal of carbamazepine and substitution with placebo and reported that 7/9 manic and 5/13 depressed patients had a partial to marked response. Several patients also showed relapses when placebo was substituted and improvement when carbamazepine was reinstituted at 600–1600 mg/d at blood levels of 8–12 μg/ml (Ballenger and Post, 1980). Two clinical trials suggest that carbamazepine at the dose of 800 mg/d with a mean plasma drug level of 8.9 μg/ml produces a significant improvement at week 2. There were more responders under carbamazepine than under placebo (41.5% vs. 22.4%) (Weisler et al., 2004, 2005, 2006).

**Acute bipolar depression**

There is only one small withdrawal study mentioned (Ballenger and Post, 1980).

**Maintenance phase**

There is only a small study on 32 patients suggesting that 60% of the carbamazepine group had a good response compared to 22.2% of the placebo group (Okuma et al., 1981).

**Randomized studies without a placebo arm**

**Acute mania**

The literature suggests that carbamazepine is generally equivalent to lithium, although somewhat more suitable for specific but difficult-to-define populations (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991). It is also suggested that it is equivalent to chlorpromazine (Okuma et al., 1979) and inferior and with slower onset of action than valproate (Vasudev et al., 2000).

**Acute bipolar depression**

No studies.

**Maintenance phase**

Several studies suggest carbamazepine is equivalent to lithium although in some of them there is a trend for lithium to perform slightly but not significantly better (Coxhead et al., 1992; Denicoff et al., 1997; Greil and Kleindienst, 1999a,b; Greil et al., 1997; Kleindienst and Greil, 2002; Lusznat et al., 1988; Placidi et al., 1986; Simhandl et al., 1993; Small et al., 1991; Stoll et al., 1989; Watkins et al., 1987).

However, the most important studies comparing carbamazepine with lithium were the MAP study in 1997 (Greil et al., 1997; Kleindienst and Greil, 2000) and a replication in 2003 (Hartong et al., 2003). They were both open studies on mixed populations and they both showed a superiority of lithium over carbamazepine for the treatment of classic mania. A secondary analysis of the MAP data showed that patients unresponsive to lithium could have a favourable response to carbamazepine (Greil et al., 1998) although its true long-term efficacy is questioned.

Combination of lithium + carbamazepine might not produce further improvement for patients although rapid-cycling patients do better under combination than under monotherapy (28.0% responded to lithium; 19.0% responded to carbamazepine and 56.3% to their combination) (Denicoff et al., 1997). Moreover, adding carbamazepine to lithium could further improve agitation in manic patients (Klein et al., 1984). Adding haloperidol to lithium was similar to adding carbamazepine (Small et al., 1995).

A potentially life-threatening side-effect of carbamazepine may be the Steven-Johnson syndrome and related dermatological effects.

**Lamotrigine**

**Randomized placebo-controlled studies**

**Acute mania**

There are two unpublished negative trials of 3-wk and 6-wk treatment of acute manic episodes (SCA2008 and SCAA2009).

**Acute bipolar depression**

Five trials concerning the acute depression treatment (SCA100223, SCA30924, SCA40910, SCAA2010 and SCAB2001) (Goldsmith et al., 2003) were negative concerning the primary outcomes but showed some benefit on the basis of secondary outcomes. On the basis of these secondary outcomes, the response rates against depression are reported to be 50% and are double those observed under placebo (Calabrese et al., 1999). Lamotrigine but not gabapentin was reported to be effective in a mixed unipolar-bipolar population of refractory depressives, with response rates 52% for...
lamotrigine, 26% for gabapentin and 23% for placebo (Frye et al., 2000).

Maintenance phase

Three placebo-controlled studies suggest that at doses of 50–400 mg/d, lamotrigine was equivalent to lithium and superior to placebo at prolonging the time to intervention for any mood episode in bipolar I patients who had recently experienced a manic or hypomanic episode. Lamotrigine was found to be superior to placebo at prolonging the time to a depressive episode, while lithium was superior at prolonging the time to a manic, hypomanic, or mixed episode (Bowden et al., 2003). The proportions of patients who were free of depression after 1 yr are reported to be 57% of those on lamotrigine, 46% for those on lithium and 45% for those on placebo. The respective proportions of patients free of mania after 1 yr were 77% for lamotrigine, 86% for lithium, and 72% for placebo. Thus the conclusion is that lamotrigine is predominantly effective against depression, and lithium predominantly effective against mania (Calabrese et al., 2003a). It is also effective against rapid cycling (Calabrese et al., 2000).

The post-hoc analysis confirmed that both lamotrigine and lithium were more effective than placebo in delaying the time to intervention for any mood episode in bipolar I disorder (Calabrese et al., 2006) and that lamotrigine was primarily effective against depression and lithium was primarily effective against mania. Lamotrigine does not induce mania/hypomania/mixed states, episode acceleration, or destabilize the overall course of illness (Calabrese et al., 2003b; Goodwin et al., 2004).

Randomized studies without a placebo arm

Acute mania

There is one pilot study reporting that lamotrigine to be as effective as lithium in the treatment of patients with BD hospitalized for acute mania (Ichim et al., 2000).

Acute bipolar depression

One study suggests that OFC is somewhat superior to lamotrigine although the response rates did not differ between groups (OFC 68.8% vs. lamotrigine 59.7%). The time to response was significantly shorter for OFC-treated patients (OFC 17 d vs. lamotrigine 23 d) and there were lesser ‘suicidal and self-injurious behaviour’ among OFC-treated patients (OFC 0.5% vs. lamotrigine 3.4%) (Brown et al., 2006).

Maintenance phase

No studies.

One study reports that adding lamotrigine to lithium was superior to placebo in patients with bipolar depression (Van der Loos et al., in press).

The most significant drawback of lamotrigine treatment is the need to initiate it slowly with a rate of 25 mg at 2-wk intervals in order to avoid a moderately high incidence of rash. Carbamazepine decreases lamotrigine concentrations by ~50%, and during combination therapy, lamotrigine can start with higher doses and faster titration.

Gabapentin

Case reports and uncontrolled trials suggest that gabapentin may be useful in the treatment of BD as an adjunctive agent (dose 600–6000 mg/d) but only during the maintenance phase. Placebo-controlled data concerning the acute phase are negative (Frye et al., 2000) and gabapentin can be considered only as an add-on therapy (Pande et al., 2000; Vieta et al., 2006a; Wang et al., 2002). It also might be a useful agent for the treatment of anxiety disorders that commonly accompany bipolar illness and could substitute for benzodiazepines. A significant advantage is that it is not metabolized in the liver.

Topiramate

Recently, the negative results of four controlled trials concerning the use of topiramate against acute mania were published (Kushner et al., 2006). Data as an adjunctive therapy are also negative, in spite of some positive reports (Roy Chengappa et al., 2006). What is unique with topiramate is its ability to cause weight loss at doses of 50–200 mg/d. It is reported that more than 70% of patients taking topiramate for a mean duration of 5 months lost a mean of 5–6 kg. Thus topiramate could be useful to treat weight gain which is a common problem in bipolar patients (Arnone, 2005).

There are no reliable data concerning the other anticonvulsant agents, although there are open studies and case reports including complicated cases (Oulis et al., 2007). A recent placebo-controlled trial reports some advantages in secondary measures of adjunctive oxcarbazepine vs. placebo in highly relapsing patients (Vieta et al., 2008). Recent trials with licarbazepine have not been reported yet.

A point that needs to be stressed is that while anti-psychotics seem to possess a ‘class effect’ restricted to
the treatment of acute mania (possibly an antidiopaminergic effect) (Brugue and Vieta, 2007), there is no such effect in anticonvulsants concerning any phase of BD. Each anticonvulsant may possess a very distinct mode of pharmacological action and should be considered separately. The mode of action of anticonvulsants in BD is unknown.

**Tamoxifen**

Tamoxifen is a selective oestrogen receptor modulator which is used in the treatment of breast cancer. It is cited along with anticonvulsants in the current review under the framework that it acts against acute mania by inhibiting protein kinase C (PKC) (Einat et al., 2007; Manji and Chen, 2002).

Two pilot, placebo-controlled studies suggest it is more effective against acute mania than placebo (Kulkarni et al., 2006; Zarate et al., 2007). A NIMH-sponsored clinical trial commenced in 2001 (ClinicalTrials.gov Identifier: NCT00026585) but the results are yet to be announced. A second trial sponsored by the Stanley Medical Research Institute (ClinicalTrials.gov Identifier: NCT00411203) led to one 3-wk, small (66 patients), placebo-controlled trial suggesting that 40–160 mg/d tamoxifen is effective against acute mania at doses and remarkably well tolerated (Yildiz et al., 2008).

**Antidepressants**

Although antidepressants have an established efficacy against unipolar depression, this fact does not unequivocally concern bipolar depression.

The earlier placebo-controlled studies suggested that amitriptyline was equivalent to lithium (Glen et al., 1984) but imipramine was inferior to it during all phases of bipolar illness, while adding imipramine does not improve the outcome (Kane et al., 1982; Prien et al., 1973b, 1984). Later randomized, placebo-controlled studies reported that 86% of the fluoxetine-treated patients improved compared with 57% of the imipramine-treated and 38% of the placebo-treated (Cohn et al., 1989) patients. Another study suggested that fluoxetine is effective both during the acute and the maintenance phase for bipolar II patients (Amsterdam et al., 1998; Amsterdam and Shults, 2005a) and after 6 months treatment 43% of fluoxetine-treated patients and 100% of placebo-treated bipolar II patients relapsed (Amsterdam and Shults, 2005b). As previously mentioned, OFC is effective against bipolar depression (Tohen et al., 2003c) and may be somewhat superior to lamotrigine (Brown et al., 2006). Only a small, placebo-controlled, crossover study suggests that SSRIs might be superior to placebo as monotherapy (Parker et al., 2006). Conversely, one of the quetiapine bipolar depression trials had a paroxetine monotherapy arm which failed to separate from placebo (McElroy et al., 2008).

Studies without a placebo arm suggested both paroxetine and venlafaxine are effective (Vieta et al., 2002), and that adding paroxetine (Young et al., 2000) or citalopram (Sachs et al., 2007b) to a mood stabilizer might improve the outcome without a significant rate of switch to mania or hypomania, however, placebo-controlled studies have not confirmed these findings. Studies comparing the response rates of bipolar vs. unipolar depression report the rates to be similar (Amsterdam and Garcia-Espana, 2000; Amsterdam et al., 1998).

A problem with antidepressant use in BDs is the potential risk to induce the opposite pole, mixed episodes and rapid cycling. Adjunctive studies report that around 14% of bipolar depressed patients under both an antidepressant and a mood stabilizer switch to mania or hypomania (Post et al., 2001, 2006). The meta-analysis suggests a higher switch rate for venlafaxine compared to SSRIs, however, the studies included were randomized trials of adjunctive treatment, possibly including more refractory patients (Leverich et al., 2006). It seems that without the concomitant use of an antimanic agent the switch rate is around 25% (Bottlender et al., 2001). In a recent double-blind, placebo-controlled study, 179 bipolar depressed patients were randomly assigned to receive up to 26 wk treatment with a mood stabilizer + adjunctive antidepressant therapy or a mood stabilizer + placebo. Recovery rates were similar (23.5% in the antidepressant group vs. 27.3% in the placebo group). Switch rates were also similar. Thus, this study does not support the usefulness of adjunctive antidepressant therapy (Sachs et al., 2007b), and it is in accord with earlier reports (Nemeroff et al., 2001). Recent placebo-controlled studies suggest no increase in switch rates after fluoxetine monotherapy and report that rates for patients under fluoxetine, olanzapine, OFC and placebo ranged from 0 to 6.7% but were not significantly different (Amsterdam and Shults, 2005a; Keck et al., 2005).

**Psychological treatments**

Hard data concerning the effectiveness of psychosocial interventions in BD are emerging. A recent RCT of cognitive therapy (CT) in 52 bipolar patients for 6 months reported that at the end of the study the CT
group had lower depression scores and less dysfunctional attitudes. A number of positive trends towards better overall outcome even at 12 months were also reported (Ball et al., 2006). Another RCT on 293 patients concerning the effectiveness of family-focused therapy, interpersonal and social rhythm therapy, and cognitive behaviour therapy on bipolar depression suggested that patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64.4% vs 51.5%) and shorter times to recovery than patients in collaborative care. No statistically significant differences were observed in the outcomes of the three intensive psychotherapies (Miklowitz et al., 2007b). More data are available concerning psychoeducation which seems to emerge as the first line of psychosocial intervention. Accumulated data have shown that psychoeducation, family-focused psychoeducation, and cognitive behavioural therapy seem to be the most efficacious interventions in the prophylaxis from recurrences in medicated bipolar patients and can help the patient and family members to learn to identify early warnings of evolving episodes so that earlier treatment can occur and triggering factors can be identified (Colom et al., 2003a,b, 2004, 2005; Reinares et al., 2004; Scott et al., 2007).

Other agents and therapeutic modalities

Benzodiazepines can be used as adjunctive medication. They are not considered effective against bipolar illness itself, however, they could be useful because of their anti-anxiety and sedative properties. Their major problem is addiction and tolerance as well as many interactions with other medications.

Dopaminergic agents and especially pramipexole could be useful in the treatment of bipolar depression either as monotherapy or as add on therapy (Zarate et al., 2004). Inositol could also be used as an augmenting agent in refractory depressive patients (Eden Evins et al., 2006). Recently a placebo-controlled study of adjunctive modafinil has been shown to improve the outcome of bipolar depression without switching to mania or hypomania (Frye et al., 2007), however subclinical switches might be present (Fountoulakis et al., 2005).

Older clinical observations and some more recent clinical trials support the efficacy of electroconvulsive therapy (ECT) in acute mania, although there are no definite data (Daly et al., 2001; Sikdar et al., 1994; Small et al., 1988). Transcranial magnetic stimulation (rTMS) of the brain at 20 Hz over the right but not left frontal cortex or 1 Hz bi-frontally is reported to be effective. However, data are still insufficient and no conclusions can be drawn (Dolberg et al., 2002; Nahas et al., 2003; Saba et al., 2004).

Existing treatment guidelines for BD

Several papers with treatment guidelines for BD have been published up to recent times. An extensive review of them can be found elsewhere (Table 1) (Fountoulakis et al., 2005). Since then more guidelines have been published raising the number of papers with guidelines to 33 (Anon, 1997; AACAP, 1997; Allen et al., 2001; APA, 1994, 1995, 2002; Barreira et al., 1999; Bauer et al., 1999; Dennehy, 2000; Frances et al., 1996; Gilbert et al., 1998; Goldberg, 2000; Goodwin et al., 1997; Goodwin, 2003; Grunze et al., 2002, 2003, 2004; Hirschfeld, 2005; Jobson, 1997; Kusumakar et al., 1997; Licht et al., 2003; McClellan and Werry, 1997; Montgomery, 2001; O’Dowd, 2006; Rush et al., 1999, 2003; Sachs et al., 2000; Suppes et al., 1995, 2001, 2002, 2003; Yatham et al., 2005, 2006). Additionally, there are a significant number of guidelines developed by national bodies and published in local papers and languages. It seems there is a trend concerning a gradual acceptance of the use of atypical antipsychotics as monotherapy and of antidepressants for a limited period of time, and always in combination with antimanic agents. The CANMAT (Yatham et al., 2006) and the NICE (O’Dowd, 2006) guidelines are the most recent but even these fail to incorporate all recent findings and approvals.

The greatest problem that guidelines face is second-line recommendation, i.e. what is next after monotherapy when first-line agents fail (Vieta et al., 2005c). Our knowledge concerning the choice of the first-line agent (among lithium, valproate, carbamazepine and atypical antipsychotics) is insufficient, although significant cues exist. Guidelines do not utilize the longitudinal history of the illness on the individual patient in the planning of therapy; on the contrary they rely heavily on the index episode. Guidelines also insist on suggesting monotherapy as the first option, although data suggest that such an approach is effective in less than half of patients and is likely to leave residual symptoms. It is true that guidelines sacrifice much effectiveness in favour of safety and less adverse effects, however, the fact is that suboptimally treated bipolar illness is a potentially lethal disease and a disabling one.

Discussion

The grading of data concerning each treatment modality for the different phases of BD is shown in Table 2.
Table 1. The recommendations by some of the guidelines for the treatment of bipolar disorder (Note: some of these guidelines were published before risperidone, quetiapine, ziprasidone and aripiprazole received FDA approval for acute mania and quetiapine and OFC for acute depression)

<table>
<thead>
<tr>
<th></th>
<th>Acute mania</th>
<th>Acute bipolar depression</th>
<th>Maintenance treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMAP (2002)</td>
<td>1st line: Li, Vp, Olz</td>
<td>1st line: Li, Vp, Olz, Li/Vp/Olz + SSRI/La</td>
<td>1st line: Li, Vp, Olz, monotherapy or + AD (intermittent use)</td>
</tr>
<tr>
<td></td>
<td>2nd line: Various combinations of two first-choice agents</td>
<td>2nd line: Various combinations of two or more first-choice agents, ECT</td>
<td>2nd line: Various combinations of two or more first-choice agents</td>
</tr>
<tr>
<td>WFSBP (2003)</td>
<td>1st line: Li, Vp, Olz, Ris, Cbz</td>
<td>1st line: AD + MS, SSRIIs + Li/La/Vp/Cbz</td>
<td>1st line: After depression: AD + MS, SSRIIs + Li/La/Vp/Cbz, After mania: Li, MS, AP</td>
</tr>
<tr>
<td></td>
<td>2nd line: Combinations of MS + aAPs, ECT</td>
<td>2nd line: Combination of first-choice agents, augmentation strategies, ECT</td>
<td>2nd line: Combination of first-choice agents</td>
</tr>
<tr>
<td>APA (2002, 2007)</td>
<td>1st line: Severe: Li/Vp + AP</td>
<td>1st line: Li, La, Li + AD, ECT</td>
<td>1st line: Li, Vp, possibly Cbz, La, Ocbz. Continue the treatment proved efficient during the acute phase</td>
</tr>
<tr>
<td></td>
<td>Mild-Mod: Li, Vp, Olz</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd line: Various combinations of two first-choice agents, ECT</td>
<td>2nd line: ECT, Combination of first-choice agents. AP should be discontinued</td>
<td>2007 update: Li, Vp, La, ECT</td>
</tr>
<tr>
<td></td>
<td>2007 update: Li for classic mania, Vp for mixed episodes, Cbz, Olz, Li/Vp + AP, ECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANMAT (2007)</td>
<td>1st line: Li, Vp, Olz, Ris, Quet, Arip, Zip, Li/Vp + Ris/Quet/Olz</td>
<td>1st line: Li, La, Li/Vp + SSRI, Olz + SSRI, Li/Vp + Bupr, Quet</td>
<td>1st line: Li, La, Vp, Olz</td>
</tr>
<tr>
<td></td>
<td>2nd line: Cbz, Ocbz, ECT, Li + Vp</td>
<td>2nd line: Quet + SSRI, Li/Vp + La</td>
<td>2nd line: Cbz, Li + Vp/Cbz, Li/Vp + Olz, Arip, Ris, Quet, Zip, Li + Ris/Quet, Li + La/SSRI/Bupr, OFC</td>
</tr>
<tr>
<td></td>
<td>3rd line: Hal, Clpz, Li/Vp + Hal, Li + Cbz, Cloz</td>
<td>3rd line: Cbz, Olz, Vp, Li + Cbz, Li + Pramx, Li/Vp + Venf, Li + MAOI, ECT, Li/Vp/AAP + TCA, Li/Vp/Cbz + SSRI + La, adjunctive EPA/riluzole/topiramate</td>
<td>3rd line: Adjunctive flupenthixol, Gabapentin, topiramate, AD</td>
</tr>
<tr>
<td>NICE (2006)</td>
<td>1st line: Severe: Olz, Quet, Ris. Li/Vp only in patients that previously responded to these agents BZ if necessary Milder forms: Li/Vp</td>
<td>1st line: SSRI + AM</td>
<td>1st line: Discontinuation of Ads, keep Li/Olz/Vp</td>
</tr>
<tr>
<td></td>
<td>2nd line: Li/Vp + APP</td>
<td>2nd line: SSRI + Li/Vp + Quet, Mrz/Venf + AM</td>
<td>2nd line: Combinations of first-line agents.</td>
</tr>
<tr>
<td></td>
<td>3rd line: ECT</td>
<td>3rd line: ECT</td>
<td>3rd line: Combinations of first-line agents plus La/Cbz</td>
</tr>
</tbody>
</table>

AAPs, Atypical antipsychotics; AD, antidepressants; AM, antimanic agents; APs, antipsychotics; Arip, aripiprazole; BZ, benzodiazepines; Bupr, bupropione; Cbz, carbamazepine; ECT, electroconvulsive therapy; EPA, eicosapentaenoic acid; La, lamotrigine; Li, lithium; MAOI, monoamine oxidase inhibitor; Mrz, mirtazapine; MS, mood stabilizers; Ocbz, oxcarbazepine; OFC, Olanzapine-fluoxetine combination; Olz, olanzapine; Pramx, pramipexole; Quet, quetiapine; Ris, risperidone; SSRIIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; Venf, venlafaxine; Vp, valproic; Zip, ziprasidone.
The earlier studies suggest a high effectiveness for older agents and a high prevalence of switching with antidepressants, which is not confirmed by the newer studies. On the other hand, these old agents are considered to be the ‘gold standard’ and are used as comparators in randomized trials of newer drugs. Since some of these studies are superiority ones, the literature could include data which might be misleading concerning the older agents and be in favour of newer drugs. This is a bias inherent in the literature and it should be taken into consideration when interpreting the data. Another possible source of bias is the fact that currently the use of lithium is much more widespread and patients with a favourable response are unwilling to participate in a study with the risk of dropping it. This fact might have led to the inclusion of a disproportionate percentage of refractory to lithium patients and also of patients suffering from milder symptomatology in the most recent studies (Burgess et al., 2001). Another problem with recent trials is the high drop-out rate which limits the generalizability of the results (Rendell et al., 2003, 2006). Those high attrition rates, however, may be in part attributable to higher ethical standards in modern studies.

Historically, the modern treatment of bipolar illness starts with lithium when Frederik Lange in the late 19th century (Lange, 1894), and later John Cade in 1949 (Bech, 2006; Cade, 1949, 1970) used it for the treatment of affective patients. However, Mogens Schou established the effectiveness of lithium for the treatment of BD (Schou, 1997; Schou et al., 1954) together with Poul Christian Baastrup (Baastrup, 1964; Baastrup and Schou, 1967; Schou and Baastrup, 1967) by performing among other things a placebo-control discontinuation study (Baastrup et al., 1970). It is widely accepted that lithium possesses a specific anti-suicidal effect (Baldessarini et al., 2003b; Bech et al., 1982; Calabrese et al., 2006; Geddes et al., 2004; Grunze et al., 2004; Kane et al., 1982; Kessing et al., 2005; Prien et al., 1984) and this is supported by a systematic review (Cipriani et al., 2005), although there is some concern that there was an over-interpretation of data (Connemann, 2006). However, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study results do not support this (Goldberg et al., 2005).

Table 2. Grading of data on the basis of a modified POST method. When the data are positive, the respective letter appears in the table. If they are negative then ‘neg’ is cited. Levels C and D suggest the need for further study.

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Acute mania</th>
<th>Acute bipolar depression</th>
<th>Maintenance treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>A</td>
<td>neg</td>
<td>A^a</td>
</tr>
<tr>
<td>Asenapine</td>
<td>A</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>A</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>B</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clozapine</td>
<td>C</td>
<td>–</td>
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<tr>
<td>ECT</td>
<td>C</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>–</td>
<td>A</td>
<td>A^b</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>neg</td>
<td>–</td>
<td>C^c</td>
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<tr>
<td>Haloperidol</td>
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<tr>
<td>Lamotrigine</td>
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<td>A^b</td>
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<tr>
<td>Lithium</td>
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<tr>
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<td>A</td>
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<tr>
<td>Olanzapine–fluoxetine combination</td>
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<td>A^e</td>
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<tr>
<td>Oxcarbazepine</td>
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<td>C</td>
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<tr>
<td>Perphenazine</td>
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<tr>
<td>Quetiapine</td>
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<td>A</td>
<td>A</td>
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<tr>
<td>Risperidone</td>
<td>A</td>
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<tr>
<td>Tamoxifen</td>
<td>A^c</td>
<td>–</td>
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<tr>
<td>Topiramate</td>
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<tr>
<td>Ziprasidone</td>
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<tr>
<td>Cognitive behavioral therapy</td>
<td>–</td>
<td>B</td>
<td>E</td>
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<tr>
<td>Psychoeducation</td>
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**Level A**: Good research-based evidence, supported by at least one placebo-controlled study of sufficient magnitude. If there are non-placebo trials controlled with a comparator and with different results, the placebo-controlled trial is the only taken into consideration.

**Level B**: Fair research-based evidence, from at least one randomized, double-blind controlled trial which, however, fail to fulfill all the criteria above (e.g. very small sample size or no placebo control).

**Level C**: At least one double-blind study with placebo or not, with a special design (e.g. ABA, discontinuation studies, etc.), or at least one open-label study with comparator or prospective open-label study, or two prospective open-label studies with >10 participants.

**Level D**: Recommendation based on prospective case studies with a minimum of 10 patients, or large-scale retrospective chart analyses and support by expert opinion.

E: Equivocal data; neg, negative data.

^a No effectiveness against bipolar depression; ^b no effectiveness against mania; ^c relatively small study sample or pilot study.
a lithium discontinuation-induced refractoriness is also reported in up to 15% of patients (Post et al., 1992). Patients with an episodic course with euthymic intervals, and the absence of rapid cycling may respond better to lithium (Bowden et al., 2000b; Faedda et al., 1991; Grof, 2003; Grof et al., 1994, 2002). It is unclear whether after prolonged treatment it exerts a neuroprotective or a neurotoxic effect (Fountoulakis et al., 2008c) and its mode of action is unclear (Wu et al., 2004). Adverse effects are to be expected during lithium therapy (Silverstone et al., 2005). Fewer than 20% of patients have no adverse effects, but only ~30% have more than minor complaints. The most frequent adverse effects include neurological, endocrinological (usually from the thyroid), cardiovascular, renal, gastrointestinal, haematological, dermatological manifestations and lithium intoxication.

Not all anticonvulsants are useful in the treatment of bipolar illness, and there is no class effect for this group in BD in spite of what many clinicians believe. Both valproate and carbamazepine are approved by the U.S. Food and Drug Administration (FDA, 2006) for the treatment of acute manic episodes. Valproate therapeutic serum concentration is 50–150 mg/ml while with carbamazepine the typical dose to treat mania is 600–1800 mg/d (blood concentration 4–12 mg/ml). The response rate against acute mania is around 50%, vs. a placebo effect equal to 20–30%. After several weeks under carbamazepine, hepatic enzyme (CYP 3A4) induction occurs, that lowers drug levels and may require additional upward dose titration (Bertilsson and Tomson, 1986). The dose-related adverse effects include double or blurred vision, dizziness, sedation, ataxia, and diplopia, vertigo, gastrointestinal disturbances, cognitive impairment, haematological effects (Blackburn et al., 1998; Tohen et al., 1991, 1995). A different case is lamotrigine, which is approved only for maintenance treatment. Several experts and drug licensing authorities do not consider the data sufficiently strong (Brown et al., 2006) to merit an acute bipolar depression label. In spite of this, response rates against depression are reported to be 50% and are double those observed under placebo (Calabrese et al., 1999). It should be noted that in this last study, the authors mainly report the secondary outcomes of the SCAB2001 trial, which were positive, in contrast to the primary outcomes which were negative. Because of a moderately high risk of rash, lamotrigine treatment should be initiated slowly with 25 mg/d for the first 2 wk and then 50 mg/d for another 2 wk.

The most recent advances in bipolar treatment concern the use of second-generation antipsychotics (SGAs). The FDA (2006) has already approved five SGAs for the treatment of acute mania: olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole. These drugs are also approved for the treatment of mania in most European countries. Quetiapine currently is the only SGA with an FDA indication against both acute mania and bipolar depression as monotherapy. Olanzapine is approved for mania and the maintenance phase, and OFC for depression, while aripiprazole is also approved for mania and the maintenance phase. First-generation (typical) antipsychotics (FGAs) and especially haloperidol, were used for long periods, especially for the treatment of acute mania, and were considered to act faster than mood stabilizers, however, the anecdotal clinical impression that many psychiatrists have is that they induce depression was recently supported by two studies (Tohen et al., 2003a; Zarate and Tohen, 2004). A recent review suggests that the magnitude of improvement was similar whether the SGAs were utilized as monotherapy or adjunctive therapy (Perlis et al., 2006b). If the patient has a life history of predominant manic or mixed episodes with rare and short depressive episodes, the administration of an SGA alone could be enough to control the disorder (Colom et al., 2006).

The biggest problem with some of the SGAs is weight gain, hyperlipidaemia and diabetes in a significant percentage of the patients receiving them. Various strategies have been developed to cope with these problems, with rather unsatisfactory results so far.

The most controversial of all classes of agents used in BD is antidepressants. Fluoxetine is the only antidepressant with official approval by the FDA for use in BD, not as monotherapy, but in combination with olanzapine. The use and usefulness of antidepressant agents in BD is controversial. Even their true effectiveness has been questioned, in spite of the randomized studies and the conclusion of a recent systematic review (Gijssman et al., 2004). Guidelines suggest their cautious use and always in combination with an antimanic agent (Fountoulakis et al., 2005). This is because antidepressants are believed to induce switching to mania or hypomania (Leverich et al., 2006; Moller et al., 2001; Post et al., 2001, 2006), mixed episodes (Himmelhoch et al., 1976) and rapid cycling, while research suggests that the use of antimanic agents might protect from such an effect (Bottlender et al., 2001). The addition of an antidepressant in patients receiving mood stabilizers could improve the outcome of depression without altering significantly the risk to switch (Young et al., 2000). Earlier studies highlighted this problem especially with tricyclics.
has already produced important insight into bipolar disorder: a systematic review of antidepressant use. The recent STEP-BD study produced equivocal results, indicating that the presence of suicidal ideation was similar between patients who were taking any lithium (22.2%) and those who were not (25.8%) and between those who were taking any valproate (20.3%) and those who were not (21.5%). Suicidal ideation was significantly more prevalent among patients who were taking a SGA (26%) than those who were not (17%) and those who were taking an antidepressant (25%) and those who were not (14%). Thus rates were similar across agents but a bias concerning the prescription strategies makes the interpretation of these results difficult (Goldberg et al., 2005). The comparison of outcomes in 335 patients who received a mood-stabilizing agent with an antidepressant vs. without an antidepressant for a bipolar depressive episode accompanied by at least two concurrent manic symptoms suggested that adjunctive antidepressant use neither hastened nor prolonged time to recovery once potential confounding factors were taken into consideration (Goldberg et al., 2007). A second study clearly supports this conclusion (Sachs et al., 2007b). However, two other studies reported an increased number of episodes in patients under antidepressants (Schneck et al., 2008) and this was especially higher in bipolar patients with short illness duration, multiple past antidepressant trials, and past experience of switch with at least one antidepressant (Truman et al., 2007). The pattern of psychopharmacological treatment at baseline for the first 500 patients suggested that standard mood stabilizers (lithium, valproate, carbamazepine) were the most commonly prescribed class of drugs that participants were taking at intake (71.9%), followed by antidepressants (40.6%), novel anticonvulsants (31.8%), SGAs (27.2%), and benzodiazepines (25%) with 11% being under standard mood-stabilizer monotherapy (Ghaemi et al., 2006). Intensive psychosocial treatment enhances relationship functioning and life satisfaction among stabilized patients with BD under pharmacotherapy (Miklowitz et al., 2007a). No real improvement was detected in refractory bipolar depressive patients after open-label augmentation with lamotrigine, inositol, or risperidone, although the concomitant use of an antimanic agent (atypical antipsychotic or anticonvulsant) may protect against switching or mixed symptoms, but this does not always happen (Moller et al., 2001; Privitera and Maharaj, 2003). However, on the contrary, in patients more prone to experience depressive episodes the continuation of treatment with antidepressants might be beneficial (Altshuler et al., 2001, 2003). The STEP-BD is a multi-center NIMH project and has already produced important insight into bipolar illness and its treatment. The assessment of the first 2000 participants followed for 18 months reported that 425 experienced a prospectively observed, new-onset major depressive episode without initial suicidal ideation and 24 participants (5.6%) developed new-onset suicidality at follow-up, including two suicide attempts. There was no association of new-onset suicidality with increased antidepressant exposure or any change in antidepressant exposure, and no association with initiation of antidepressant treatment (Bauer et al., 2006). The assessment of 1000 patients revealed that the presence of suicidal ideation was similar between patients who were taking any lithium (22.2%) and those who were not (25.8%) and between those who were taking any valproate (20.3%) and those who were not (21.5%). Suicidal ideation was significantly more prevalent among patients who were taking a SGA (26%) than those who were not (17%) and those who were taking an antidepressant (25%) and those who were not (14%). Thus rates were similar across agents but a bias concerning the prescription strategies makes the interpretation of these results difficult (Goldberg et al., 2005). 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lamotrigine performed somewhat better (Nierenberg et al., 2006).

Most authors agree that after the second episode of bipolar illness, long-term treatment is necessary, but this may still be too conservative, with most patients actually benefiting from early lifelong therapy. This treatment is based on the use of lithium, aripiprazole, olanzapine or OFC, quetiapine and lamotrigine either as monotherapy or in combination. Traditional choices like valproate do not have sufficient scientific support. The choice depends largely on the longitudinal course of the illness and the predominant polarity of the episodes as well as previous response to a specific agent. Although it has been claimed that maintenance treatment should last at least 2 yr after an episode or 5 yr if the patient has risk factors for relapse (O’Dowd, 2006), in clinical practice it is better to plan for lifetime treatment unless contraindications or specific issues indicate otherwise.

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**Statement of Interest**

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