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REVIEW/MINI-REVIEW ▸

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania

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Summary
Identical to the preceding guidelines of this series, these practice guidelines for the biological, mainly pharmacological treatment of acute bipolar mania were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). Their purpose is to supply a systematic overview of all scientific evidence pertaining to the treatment of acute mania. The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, from recent proceedings of key conferences, and from various national and international treatment guidelines. Their scientific rigor was categorised into four levels of evidence (A-D). As these guidelines are intended for clinical use, the scientific evidence was finally not only graded, but has also been commented by the experts of the task force to ensure practicability.

Key words: *bipolar disorder, mania, acute treatment, evidence-based guidelines, pharmacotherapy, antipsychotics, mood stabiliser, electroconvulsive therapy.*

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Introduction and Methods

This part of the WFSBP guidelines for the pharmacological treatment of bipolar disorder is dedicated to mania. The background and reasons for establishing these treatment recommendations were explained in the first part, dedicated to the treatment of bipolar depression (Grunze et al. 2002). In brief, the following grading of

evidence based on the Schizophrenia Patient Outcome Research Team (PORT) treatment recommendations (Lehman and Steinwachs 1998) was established, combining evidence-based elements and clinical experience, and used in both the WFSBP guidelines on bipolar (Grunze et al. 2002) and those on unipolar (Bauer et al. 2002) affective illness:

Level A: Good research-based evidence. This means that evidence for efficacy has been proven by at least three methodologically good trials, including at least one placebo-controlled trail and at least two comparison trials with another standard treatment. In these trials, criteria such as sufficient sample size, duration of trial, randomised distribution to either treatment and double-blind conditions should have been obeyed.
Level B: Fair research-based evidence. On the basis of trials, this includes evidence from at least two randomised, DB-controlled trials which, however, fail one criterion to fulfil the criteria above (e.g., small sample size or no placebo control) or from 1 RDB study and at least 1 prospective, large scale naturalistic study.
Level C: 1 RDB study with comparator, 1 prospective open label (POL) study, or 2 POLs with >10 participants.
Level D: Recommendation based on prospective case studies with a minimum of ten patients or large scale retrospective chart analyses and support by expert opinion.

According to clinical opinion, acute mania can be differentiated into euphoric (classical) mania, dysphoric mania, mixed states, mania with psychotic or catatonic features, and mania within a rapid cycling course of the disease. If these subtypes can be shown reliably to exist (Dilsaver et al. 1999), they may influence not only classification but also the choice of treatment.

Clinical experience with the various tentative mood stabilisers over recent years has suggested that a drug that is efficacious in one manifestation of mania is not necessarily the treatment of choice for the overall spectrum of mania. In recognition of this sentiment, these treatment algorithms will also distinguish between euphoric (classical) mania, dysphoric mania and mixed states, psychotic mania, mania within a rapid cycling course of bipolar disorder and, finally, hypomania. However, words of caution are necessary. Manic states are certainly not monolithic, but neither are they likely to reflect neat clinical distinctions. Recent factor analysis of symptoms in mania suggested that there are perhaps five factors that contribute to the syndrome (Cassidy et al. 1998). The first and strongest factor represented dysphoria in mania, with strong positive loadings for depressed mood, lability, guilt, anxiety and suicidal thoughts and behaviours, and a strong negative loading for euphoric mood. Factors 2 through 5 represented psychomotor acceleration, psychosis, increased hedonic function and irritable aggression, respectively. The distribution of weighted scores on factor I was bimodal, whereas the corresponding distributions of factors 2 through 5 were unimodal. No general factor denoting overall severity of mania was found. These results were from a modest sized sample. Subsequently the same authors have claimed that Grade of Membership (GOM) analysis revealed five 'pure types' with good face validity. The major new finding was of two mixed mania presentations. The first of these displayed a dominant mood of severe depression with labile periods of pressured, irritable hostility and paranoia, and the complete absence of euphoria or humour. The second mixed mania displayed a true, incongruous mixture of affects: periods of classical manic symptoms with euphoria, elation, humour, grandiosity, psychosis, and psychomotor activation, switching frequently to moderately depressed mood with pressured anxiety and irritability. DSM-III-R criteria (used to classify the patients originally) did not reliably identify either of these two natural groups of mixed bipolar patients (Cassidy et al. 2001). While different sub-classes of mania may exist, all the extant data on differential treatment response represent potentially unreliable secondary analysis of data sets lacking power to prove that different responses to different treatments are real, not imaginary.

Treatment of acute mania

• Euphoric (classical) mania

Traditionally, bipolar I disorder with euphoric mania was considered as the classical and, for a long time, only type of mania that justifies the diagnosis of bipolar disorder. Other manifestations within the bipolar spectrum, e.g. bipolar II disorder or bipolar disorder with psychotic mania, were often classified either as recurrent depression or schizophrenia. Until recently, most studies on antimanic agents were exclusively conducted in patients with bipolar I disorder and euphoric mania, resulting in firm evidence that especially lithium is effective in this type of mania. Our literature search found 26 studies, of which at least 13 are controlled trials in which lithium showed superior or equal efficacy compared to placebo (five trials), antipsychotics, carbamazepine or valproate in the treatment of acute euphoric mania (for a review, see Bowden 1998; Poolsup et al. 2000; McElroy et al. 1996b). The only methodological pitfall is that, so far, only one three-arm study with placebo control and active comparator has been published for lithium (Bowden et al. 1994). Nevertheless, with evidence considered, lithium can be seen as a first line treatment in euphoric mania within classical bipolar I disorder (level A). Other level A qualifying treatments include in particular valproate (Emrich et al. 1980; Freeman et al. 1992; Pope et al. 1991; Bowden et al. 1994) and some atypical antipsychotics,

especially olanzapine (Tohen et al. 1999; Tohen et al. 2000). Compared to lithium, valproate has a more rapid onset of action as valproate's wide therapeutic window allows loading treatment strategies (Keck et al. 1993). When compared directly to lithium, valproate showed approximately equal efficacy (Bowden et al. 1994; Emilien et al. 1996). Especially in patients with numerous (>8) episodes in history (Swann et al. 2000a), or >4 depressive episodes (Swann et al. 2000b) and who have failed on lithium prophylaxis, valproate may be the preferred choice in the treatment of acute euphoric mania.

Recently, the atypical antipsychotics olanzapine (Tohen et al. 1999; Berk et al. 1999; Tohen et al. 2000) and risperidone (Sachs et al. 2002; Yatham 2000; Segal et al. 1998) supplied Level A evidence for antimanic efficacy. Also ziprasidone has shown antimanic properties in an unpublished controlled trial in bipolar patients (Keck and Ice 2000, Level C). Olanzapine has already been approved by the FDA for the treatment of mania.

There are doubts about the clinical relevance of all recent placebo-controlled trials in mania. They are dominated by excessively high drop-out rates (about 50% in three weeks) and the reliance on rating scales with "last observation carried forward." Additionally, there is as yet very little experience of how the newer atypical antipsychotics compare directly to other treatment standards. Thus, for olanzapine there is a small, but not placebo-controlled study against lithium (Berk et al. 1999) and two inconclusive – due to insufficient dosages – studies against valproate. The arguments for the use of atypical antipsychotics in general are their good tolerability when used at doses recommended for schizophrenia (which may be too low for severe mania) and relatively rapid onset of action. However, their potency in treating acute mania has still to be established, especially in comparison with typical antipsychotics.

Our own literature quest found at least 17 double-blind controlled studies examining the efficacy of either carbamazepine or oxcarbazepine in acute mania, however, carbamazepine has never been tested against placebo in a parallel group design (Licht 1998). Carbamazepine may be useful in selected patients in treating euphoric mania (Level B, for a review Keck and McElroy 1996; Post et al. 1996; Emilien et al. 1996), and should be continued especially in those who have previously been on prophylactic treatment with carbamazepine. Otherwise, it does not seem to have any special advantage over the other treatment alternatives. In fact, a recent small controlled study demonstrated a better efficacy for valproate than carbamazepine in acute mania (Vasudev et al. 2000). The use of carbamazepine is also complicated by its interaction with other co-medication, e.g. antipsychotics, through effects on the cytochrome P450 system (Hesslinger et al. 1999), leading to a marked decrease of antipsychotic plasma levels and probable loss of efficacy.

Taken together, the evidence for efficacy in euphoric mania is very good (Level A) for lithium, valproate, olanzapine, risperidone, reasonable for carbamazepine (Level B) and supposedly for ziprasidone (Level C). Classical, highly potent antipsychotics are almost universally used and evidence exists that they are efficacious (Level A, for a review see Tohen and Zarate 1998; Dubovsky and Buzan 1997). This has recently been backed up by a double-blind randomised study of risperidone as add-on to mood stabilisers where haloperidol was an internal comparator (Sachs et al. In Press). In this study, haloperidol was significantly better than placebo. The position of the older antipsychotics remains anomalous because the quality of the research evidence for any given drug is individually surprisingly weak: haloperidol, for example has never been formally shown to be superior to placebo in a parallel-group monotherapy trial in mania, yet it is 'gold standard' treatment besides lithium.

However, the use of classical neuroleptics *in high dosages* should be restricted to very severe or violent cases of mania where parenteral administration is the only choice, and should be limited to a maximum of a few weeks, to avoid the risk of tardive dyskinesia (TD). TD may have an increased incidence in bipolar patients (Mukherjee et al. 1986). The aetiology of TD remains uncertain but is believed to result from long-term blockade of dopamine receptors. The true risks for atypical antipsychotics with a high degree of D2 receptor occupancy are not yet established. The key message from the introduction of the atypical drugs is that it is possible to achieve antipsychotic and anti-manic action without inducing severe extra-pyramidal side effects. This may imply that low-dose classical antipsychotics are a sensible alternative to atypical antipsychotics (Geddes et al. 2000). This may apply as much to mania as to schizophrenia.

• Dysphoric mania and mixed states

These two manifestations of mania are summarised under one heading. According to DSM-IV, mixed states imply that diagnostic criteria for a manic episode and a depressive episode (except for the duration criterion) are fulfilled simultaneously. Dysphoric mania describes mania with some depressed and dysphoric features that are either not pronounced enough or insufficiently lasting enough to fulfil the criteria for a major depressive episode. Women appear more often affected than men (Arnold et al. 2000).

As dysphoric mania and mixed states have not been the subject of intensive studies and

controlled trials so far, we have only a limited amount of evidence for the superiority of one drug over another. Thus secondary analysis of the influential valproate efficacy study (Swann et al. 1997a) as well as some older studies (Secunda et al. 1987; Himmelhoch and Garfinkel 1986) indicated that lithium may not be very effective, and that valproate, carbamazepine, olanzapine and risperidone may be more efficacious than lithium in these patients (Freeman et al. 1992; Swann et al. 1997b; Goldberg et al. 1998; Tohen et al. 2000; Benabarre et al. 2001, Level C). The use of classical antipsychotics especially in higher dose may exacerbate dysphoric or depressive experience and should probably be avoided (Whitlock and Evans 1978).

• Psychotic mania

Psychotic mania has only recently been arbitrarily designated as a subtype of bipolar mania. It is unclear whether secondary grandiose delusions – the commonest clinical manifestation of 'psychosis' merits qualitative distinction since it looks much more like an expression of severity. On the other hand, first rank symptoms also occur in mania and confuse the distinction from schizophrenia. 'Psychotic mania' is a diagnosis that conflates these perhaps different clinical conditions.

As for mixed states, so for psychotic mania evidence for superiority of one treatment over another is limited. Classical antipsychotics, in this case pimozide, may be superior to lithium as shown by the Northwick Park functional psychosis study (Johnstone et al. 1988). Some guidelines favour anticonvulsants over lithium when psychotic symptoms are present (e.g. Kusumakar et al. 1997), others recommend the combination of either valproate or lithium with an antipsychotic right from the start (Keck and McElroy 1996). As far as monotherapy studies are concerned, valproate showed equal efficacy to haloperidol in one randomised but not blinded trial in psychotic mania (McElroy et al. 1996a, Level C). Although it is tempting to assume that all atypical antipsychotics are efficacious in psychotic mania, unambiguous controlled trials are still missing. However, retrospective analysis of the two placebo-controlled trials of olanzapine and of the controlled studies involving risperidone showed similar response rates in psychotic versus non-psychotic mania (Level C).

• Severity of mania

Recent treatment recommendations from North America have almost uniformly advocated the preferential use of lithium or valproate ('mood stabilisers') for the first-line treatment of mania. Despite this, classical antipsychotics are still very widely used in manic patients. For example, more than 60 % of manic patients received classical antipsychotics at the Psychiatric University Hospital of Vienna between 1997 and 1999 (Letmaier, personal communication). In other settings, the figures may be even much higher (for example, 89 % in a Scandinavian routine setting, Licht et al. 1994).

Obviously, besides symptomatology, the severity of behavioural disturbance determines the first-line treatment in acute mania. Most treatment algorithms are based on controlled trials in mild to moderately manic patients who are still able to sign informed consent. In clinical practice, severity is more likely the primary argument in favour of a special drug. For the ultra-short treatment of acutely manic and highly excited or violent patients, classical antipsychotics still have their place (Licht 1998) and are superior to lithium (Prien et al. 1972; Garfinkel et al. 1980). In patients who are severely manic but still willing to take medication, loading with lithium (Keck et al. 2001), valproate (Keck et al. 1993; Grunze et al. 1999) or carbamazepine may be an alternative (Dose and Emrich 1995).

Although atypical antipsychotics showed efficacy in controlled trials, these trials included mild to moderate manic patients and generalisability to severe mania is difficult (Licht et al. 1997). Clinical experience with dose-loading is still missing and may be complicated by potential QT prolongation. Currently, the domain of atypical antipsychotics appears to be milder forms of mania and hypomania. An exception may be clozapine which has shown efficacy in refractory mania, both euphoric and dysphoric, in open prospective trials (Level C, Calabrese et al. 1996; Green et al. 2000; Müller and Heipertz 1977; Suppes et al. 1992; Antonacci and Swartz 1995).

• Hypomania

Hypomania usually does not need immediate intervention with a maximised treatment. The best recommendation is to check the plasma level of the mood stabiliser the patient has been taking previously and, depending on the result, increase the dosage. If the patient has not previously received a mood stabiliser, an appropriate drug should be introduced that will also be the drug of choice for prophylaxis. As many patients with hypomania may have an underlying cyclothymic disorder, drugs showing efficacy in cyclothymia should also be considered and continued for long-term treatment. Open studies suggest efficacy of low doses of lithium or valproate (Deltito 1993; Jacobsen 1993; Akiskal 2001). There is also evidence for the usefulness of risperidone in hypomania (Vieta et al. 2001). If no further prophylaxis is planned, short-term treatment with either valproate or an atypical antipsychotic may be the best choice (Level D), as both are well tolerated, have a good safety profile and a relatively rapid onset of action, minimising the danger that hypomania develops into mania within the next days.

• Mania within a rapid cycling course of bipolar disorder

The treatment of rapid cycling patients is a special challenge (Knoll et al. 1998). There is increasing awareness of the switch risk associated with the use of classical antidepressants and the risk of kindling the rapid cycling course (Wehr and Goodwin 1979; Altshuler et al. 1995). The failure of lithium treatment appears high in rapid cycling patients (Calabrese and Woyshville 1995). Unfortunately, there have been no double-blind controlled studies specifically dedicated to the acute treatment of mania within a rapid cycling course. However, there is a large bulk of open data which favour valproate for the treatment of mania within rapid cycling, with the largest naturalistic follow-up being reported by Calabrese (Calabrese et al. 1993) (Level C). Carbamazepine also has been reported to be effective in rapid cycling (Joyce 1988) (Level D). In refractory patients, clozapine (Suppes et al. 1994; Calabrese et al. 1991; Frye et al. 1996; Lancon and Llorca 1996) or a combination therapy with valproate and lithium may also be useful (Sharma et al. 1993) (Level D). If not only the acute treatment of break-through mania is an issue, but also maintenance treatment, initiation of lamotrigine with subsiding (hypo)mania can be recommended, especially in bipolar II patients (Calabrese et al. 2000).

Finally, rapid cycling appears more common in patients with hypothyroidism, and high-dose thyroid hormone augmentation may be considered already at an early stage of treatment (Bauer and Whybrow 1990; Bauer et al. 1990)

Tolerability and safety

The treatment experience is a key issue for patients and their families. It also has inevitable consequences for trust in the therapeutic relationship and compliance. Extra-pyramidal side effects (EPS) and long-term TD are the major risks of using dopamine blocking drugs. In the case of mania, high doses of classical antipsychotics, a traditional approach in many countries over many years, should not be the treatment of choice in the great majority of patients who accept medication and should only ever be used when the potential benefits definitely outweigh the known risks. Low doses up to the threshold for EPS may be acceptable, if sufficiently monitored, but increasingly we expect atypical drugs to prove preferable where they can be afforded.

Patients who take drugs irregularly, and who are at a risk of overdosing, should not be considered as candidates for lithium treatment owing to its narrow therapeutic ratio.

There is a growing awareness of the secondary impact of many long-term treatments on general physical health. Apart from being a cosmetic issue, obesity is increasingly seen as a major health issue for patients treated with drugs that promote weight gain, of which there are many examples in any bipolar guideline. While this is a concern that is most pressing in the nations of the world where obesity is already prevalent, it is a potential problem for all individuals who gain weight excessively after drug treatment. Valproate, lithium and several antipsychotics all cause significant weight gain in long-term treatment. With weight gain go other adverse metabolic effects (e.g. carbohydrate intolerance/type II diabetes and hyperlipidaemia) and hypertension. When combined with heavy smoking, an additional hazard for many patients with mood disorder, cardiovascular disease is a major long-term risk. Not only for tricyclic antidepressants, but also for a variety of antipsychotics prolongation of the QT interval may constitute a minor additional problem. Appropriate medical screening and advice should constitute part of good psychiatric care. Thus, not only efficacy is an issue when selecting the first-line treatment, but also the patient's special needs and vulnerability to side effects.

Adverse effects are otherwise specific to individual drugs and usually require drug withdrawal. Readers are referred to relevant data sheets.

When considering special populations, all classical mood stabilisers (lithium, valproate, carbamazepine) appear teratogenic in pregnancy, especially in the first trimester, and if possible use should be interrupted. On balance lithium is now believed to be safer than the anticonvulsants (Cohen et al. 1994). Benzodiazepines and typical antipsychotics have a reasonable safety profile and can be used as a rescue medication in break-through mania. There is increasing awareness of the early onset of bipolar disorder (Kessler et al. 2001). In adolescence, some experience exists with lithium, valproate, carbamazepine and atypical antipsychotics (James and Javaloyes 2001; Kowatch et al. 2000; Chang and Ketter 2000). In geriatric patients, the use of lithium should be considered very carefully due to decreased kidney function, diminished fluid intake and probably more pronounced cognitive side effects. Valproate or low dose atypical antipsychotics may be more favourable (Amann et al. 2000).

Other treatment options

Small open studies and case reports exist on numerous alternate pharmacological approaches (for example, anticonvulsants such as phenytoin, oxcarbazepine, gabapentin, clonazepam, zonisamide, topiramate; carbonic anhydrase inhibitors, PK-inhibitors (e.g. tamoxifen), omega-3 fatty acids, calcium antagonists, clonidine, methysergide, etc.), but the evidence is still very limited.

Electroconvulsive therapy (ECT) is regarded as the most efficacious treatment modality for mania, frequently chosen (and anecdotally found effective) when other approaches have failed (Small et al. 1988; Black et al. 1987; Mukherjee et al. 1994, Level C). Accordingly it should be considered in patients accepting this treatment and who have not responded to previous drug treatments. Case reports on the efficacy of transcranial magnetic stimulation in mania exist (Yaroslavsky et al. 1999; Pridmore and Belmaker 1999), but this may be difficult to conduct, at least in severely manic patients. The same may be true for more sophisticated psychotherapeutic interventions besides very basic behavioural standards (correcting sleep-wake cycle, avoid hyperstimulation, etc.).

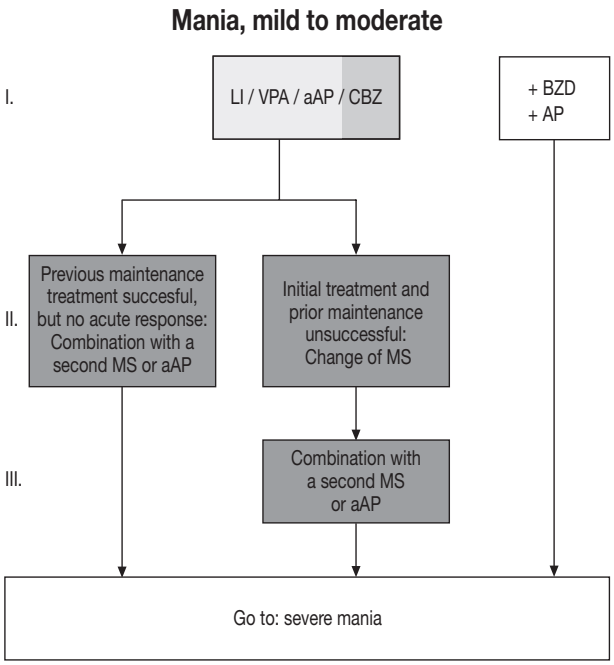
Conclusion

The most important steps in the state-of-the-art treatment of mania include

- clarification of the subtype of mania,
- considering the longitudinal course of illness,
- although treatment is often initiated against the patient's will, at a later stage the patient's compliance should be optimised by using a drug with a favourable tolerability profile for the individual patient.

If the patient has been on prophylactic treatment, with reasonable success and good tolerability so far, an increase of the dosage of this previous mood stabiliser should be considered first. Otherwise, if the patient has had no previous prophylactic treatment and prophylaxis may become an issue, the overall course of the disease should also be taken into consideration. Clearly, prophylactic treatment of a patient with classical bipolar I disorder with only rare episodes differs from prophylactic treatment in a rapid cycling patient showing additional atypical features like psychotic mania. Whereas in the first case, lithium may be the treatment of choice already for acute mania, non-classical manifestations seem to respond better to anticonvulsants and perhaps atypical antipsychotics.

Suggestions for step-wise pharmacological treatment algorithms are summarised in the Figures 1 and 2 below.

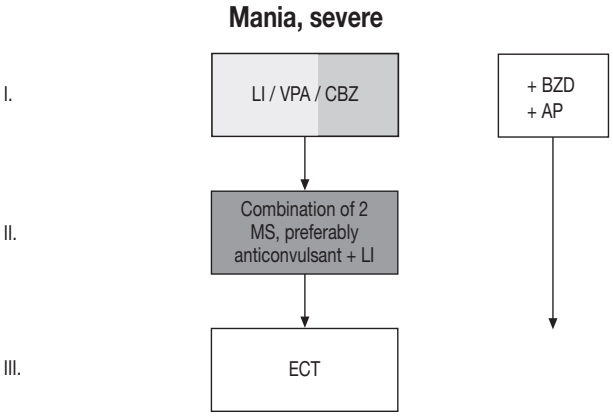


MS : Mood stabiliser
Li : Lithium
CBZ : Carbamazepine
VPA : Valproate
aAP : atypical antipsychotic (best evidence: olanzapine, risperidone)

Additionally, when needed:
BZD : Benzodiazepines
AP : Antipsychotics (preferably low potent or atypical AP)

Evidence Level A
Evidence Level B
Evidence Level C
Evidence Level D

Figure 1



MS : Mood stabiliser
Li : Lithium
CBZ : Carbamazepine
VPA : Valproate
ECT : Electroconvulsive therapy

Additionally, when needed for symptom control:
BZD : Benzodiazepines
AP : Antipsychotics (preferably atypical AP, high potent AP (also injectable) when indicated)

Evidence Level A
Evidence Level B
Evidence Level C
Evidence Level D

Figure 2

References

Akiskal H (2001) Dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. J Affect Disord 62: 31.

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L (1995) Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 152: 1130-1138.

Amann B, Schlösser S, Sterr A, Hummel B, Schäfer M, Padovan CS, Grunze H (2000) Anticonvulsants in the treatment of aggression in the demented elderly. Psychiatric Networks 3: 87-95.

Antonacci DJ, Swartz CM (1995) Clozapine treatment of euphoric mania. Ann Clin Psychiatry 7: 203-206.

Arnold LM, McElroy SL, Keck PE (2000) The role of gender in mixed mania. Compr Psychiatry 41: 83-87.

Bauer MS, Whybrow PC (1990) Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch Gen Psychiatry 47: 435-440.

Bauer MS, Whybrow PC, Winokur A (1990) Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism. Arch Gen Psychiatry 47: 427-432.

Bauer M, Whybrow PC, Angst J, Versiani M, Möller H-J, WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders (2002) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive disorder,Part 1: Acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 3: 5-43.

Benabarre A, Vieta E, Colom F, Martinez A, Reinares M, Corbella B (2001) Treatment of mixed mania with risperidone and mood stabilizers. Can J Psychiatry 46: 866-867.

Berk M, Ichim L, Brook S (1999) Olanzapine compared to lithium in mania: A double-blind randomized controlled trial. Int Clin Psychopharmacol 14: 339-343.

Black DW, Winokur G, Nasrallah A (1987) Treatment of mania: a naturalistic study of electroconvulsive therapy versus lithium in 438 patients. J Clin Psychiatry 48: 132-139.

Bowden CL (1998) Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. J Clin Psychiatry 59 (Suppl 6): 13-19.

Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsaver SC, Davis JM, Rush AJ, Small JG, Garza-Trevino ES, Risch SC, Goodnick PJ, Morris DD (1994) Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 271: 918-924.

Calabrese JR, Woyshville MJ (1995) A medication algorithm for treatment of bipolar rapid cycling? J Clin Psychiatry 56 (Suppl 3): 11-18.

Calabrese JR, Meltzer HY, Markovitz PJ (1991) Clozapine prophylaxis in rapid cycling bipolar disorder. J Clin Psychopharmacol 11: 396-397.

Calabrese JR, Woyshville MJ, Kimmel SE, Rapport DJ (1993) Predictors of valproate response in bipolar rapid cycling. J Clin Psychiatry 13: 280-283.

Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, Meltzer HY (1996) Clozapine for treatment-refractory mania. Am J Psychiatry 153: 759-764.

Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann A, McElroy SL, Kusamakar V, Ascher JA, Earl NL, Greene PL, Monaghan ET (2000) A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid cycling bipolar disorder. J Clin Psychiat 61: 841-850.

Cassidy F, Murry E, Forest K, Carroll BJ (1998) Signs and symptoms of mania in pure and mixed episodes. J Affect Disord 50: 187-201.

Cassidy F, Pieper CF, Carroll BJ (2001) Subtypes of mania determined by grade of membership analysis. Neuropsychopharmacology 25: 373-383.

Chang KD, Ketter TA (2000) Mood stabilizer augmentation with olanzapine in acutely manic children. J Child Adolesc Psychopharmacol 10: 45-49.

Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML (1994) A reevaluation of risk of in utero exposure to lithium. JAMA 271: 146-150.

Deltito JA (1993) The effect of valproate on bipolar spectrum temperamental disorders. J Clin Psychiatry 54: 300-304.

Dilsaver SC, Chen YR, Shoaib AM, Swann AC (1999) Phenomenology of mania: evidence for distinct depressed, dysphoric, and euphoric presentations. Am J Psychiatry 156: 426-430.

Dose M, Emrich HE (1995) Acute mania: Practical therapeutic guidelines. CNS Drugs 3: 427-435.

Dubovsky SL, Buzan RD (1997) Novel alternatives and supplements to lithium and anticonvulsants for bipolar affective disorder. J Clin Psychiatry 58: 224-242.

Emilien G, Maloteaux JM, Seghers A, Charles G (1996) Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. Eur Neuropsychopharmacol 6: 245-252.

Emrich HM, von Zerssen D, Kissling W, Möller H-J, Windorfer A (1980) Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. Arch Psychiatr Nervenkr 229: 1-16.

Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC (1992) A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 149: 108-111.

Frye MA, Altshuler LL, Bitran JA (1996) Clozapine in rapid cycling bipolar disorder. J Clin Psychopharmacol 16: 87-90.

Garfinkel PE, Stancer HC, Persad E (1980) A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. J Affect Disord 2: 279-288.

Geddes J, Freemantle N, Harrison P, Bebbington P (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 321: 1371-1376.

Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L (1998) Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar patients. J Clin Psychiatry 59: 151-158.

Green AI, Tohen M, Patel JK, Banov M, DuRand C, Berman I, Chang H, Zarate C, Jr., Posener J, Lee H, Dawson R, Richards C, Cole JO, Schatzberg AF (2000) Clozapine in the treatment of refractory psychotic mania. Am J Psychiatry 157: 982-986.

Grunze H, Erfurth A, Amann B, Giupponi G, Kammerer C, Walden J (1999) Intravenous valproate loading in acutely manic and depressed bipolar I patients. J Clin Psychopharmacol 19: 303-309.

Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, Vieta E, Möller HJ, WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2002) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorders, Part I: Treatment of Bipolar Depression. World J Biol Psychiatry 3: 115-124.

Hesslinger B, Normann C, Langosch JM, Klose P, Berger M, Walden J (1999) Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. J Clin Psychopharmacol 19: 310-315.

Himmelhoch JM, Garfinkel ME (1986) Sources of lithium resistance in mixed mania. Psychopharmacol Bull 22: 613-620.

Jacobsen FM (1993) Low-dose valproate: a new treatment for cyclothymia, mild rapid cycling disorders, and premenstrual syndrome. J Clin Psychiatry 54: 229-234.

James AC, Javaloyes AM (2001) The treatment of bipolar disorder in children and adolescents. J Child Psychol Psychiatry 42: 439-449.

Johnstone EC, Crow TJ, Frith CD, Owens DG (1988) The Northwick Park 'functional' psychosis study: diagnosis and treatment response. Lancet 2: 119-125.

Joyce PR (1988) Carbamazepine in rapid cycling bipolar affective disorder. Int Clin Psychopharmacol 3: 123-129.

Keck PE, Ice K (2000) Ziprasidone in acute mania. APA

Abstract Nr 224.

Keck PE, McElroy SL (1996) Outcome in the pharmacologic treatment of bipolar disorder. J Clin Psychopharmacol 16: 15S-23S.

Keck PE, McElroy SL, Tugrul KC, Bennett JA (1993) Valproate oral loading in the treatment of acute mania. J Clin Psychiatry 54: 305-308.

Keck PE, Strakowski SM, Hawkins JM, Dunayevich E, Tugrul KC, Bennett JA, McElroy SL (2001) A pilot study of rapid lithium administration in the treatment of acute mania. Bipolar Disord 3: 68-72.

Kessler RC, Avenevoli S, Ries MK (2001) Mood disorders in children and adolescents: an epidemiologic perspective. Biol Psychiatry 49: 1002-1014.

Knoll J, Stegman K, Suppes T (1998) Clinical experience using gabapentin adjunctively in patients with a history of mania or hypomania. J Affect Disord 49: 229-233.

Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ (2000) Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 39: 713-720.

Kusumakar V, Yatham LN, Haslam DR, Parikh SV, Matte R, Silverstone PH, Sharma V (1997) Treatment of mania, mixed state, and rapid cycling. Can J Psychiatry 42 (Suppl 2): 79S-86S.

Lancon C, Llorca PM (1996) Clozapine et traitement des troubles bipolaires a cycles rapides. Encephale 22: 468-469.

Lehman AF, Steinwachs DM (1998) Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 24: 1-10.

Licht RW (1998) Drug treatment of mania: a critical review. Acta Psychiatr Scand 97: 387-397.

Licht RW, Gouliaev G, Vestergaard P, Dybbro J, Lund H, Merinder L (1994) Treatment of manic episodes in Scandinavia: the use of neuroleptic drugs in a clinical routine setting. J Affect Disord 32: 179-185.

Licht RW, Gouliaev G, Vestergaard P, Frydenberg M (1997) Generalisability of results from randomised drug trials. A trial on antimanic treatment. Br J Psychiatry 170: 264-267.

McElroy SL, Keck PE, Stanton SP, Tugrul KC, Bennett JA, Strakowski SM (1996a) A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. J Clin Psychiatry 57: 142-146.

McElroy SL, Pope HG, Keck PE, Hudson JI, Phillips KA, Strakowski SM (1996b) Are impulse-control disorders related to bipolar disorder? Compr Psychiatry 37: 229-240.

Mukherjee S, Rosen AM, Caracci G, Shukla S (1986) Persistent tardive dyskinesia in bipolar patients. Arch Gen Psychiatry 43: 342-346.

Mukherjee S, Sackeim HA, Schnur DB (1994) Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry 151: 169-176.

Müller P, Heipertz R (1977) Zur Behandlung manischer Psychosen mit Clozapin. Fortschr Neurol Psychiatr Grenzgeb 45: 420-424.

Poolsup N, Li-Wan PA, De Oliveira IR (2000) Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther 25: 139-156.

Pope HG, McElroy SL, Keck PE, Hudson JI (1991) Valproate in the treatment of acute mania. A placebo-controlled study. Arch Gen Psychiatry 48: 62-68.

Post RM, Ketter TA, Denicoff K, Pazzaglia PJ, Leverich GS, Marangell LB, Callahan AM, George MS, Frye MA (1996) The place of anticonvulsant therapy in bipolar illness. Psychopharmacology 128: 115-129.

Pridmore S, Belmaker R (1999) Transcranial magnetic stimulation in the treatment of psychiatric disorders. Psychiatry Clin Neurosci 53: 541-548.

Prien RF, Caffey EM, Klett CJ (1972) Comparison of lithium carbonate and chlorpromazine in the treatment of mania. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 26: 146-153.

Sachs G, Grossman F, Okamoto A, Ghaemi SN, Bowden CL (2002) Risperidone plus mood stabilizer versus placebo plus mood stabilizer for acute mania of bipolar disorder: a double-blind comparison of efficacy and safety. Am J Psychiatry 159: 1146-1154

Secunda SK, Swann A, Katz MM, Koslow SH, Croughan J, Chang S (1987) Diagnosis and treatment of mixed mania. Am J Psychiatry 144: 96-98.

Segal J, Berk M, Brook S (1998) Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 21: 176-180.

Sharma V, Persad E, Mazmanian D, Karunaratne K (1993) Treatment of rapid cycling bipolar disorder with combination therapy of valproate and lithium. Can J Psychiatry 38: 137-139.

Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, Small IF (1988) Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry 45: 727-732.

Suppes T, McElroy SL, Gilbert J, Dessain EC, Cole JO (1992) Clozapine in the treatment of dysphoric mania. Biol Psychiatry 32: 270-280.

Suppes T, Phillips KA, Judd CR (1994) Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. Biol Psychiatry 36: 338-340.

Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, Dilsaver SC, Davis JM (1997a) Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 54: 37-42.

Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, Dilsaver SC, Davis JM (1997b) Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 54: 37-42.

Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD (2000a) Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry 156: 1264-1266.

Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD (2000b) Mania: differential effects of previous depressive and manic episodes on response to treatment. Acta Psychiatr Scand 101: 444-451.

Tohen M, Zarate CA (1998) Antipsychotic agents and bipolar disorder. J Clin Psychiatry 59 (Suppl 1): 38-48.

Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, Petty F, Centorrino F, Wang R, Grundy SL, Greaney MG, Jacobs TG, David SR, Toma V (1999) Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 156: 702-709.

Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, Sanger T, Risser R, Zhang F, Toma V, Francis J, Tollefson GD, Breier A (2000) Efficacy of olanzapine in acute bipolar mania: A double-blind, placebo-controlled study. Arch Gen Psychiatry 57/9:-849.

Vasudev K, Goswami U, Kohli K (2000) Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. Psychopharmacology Berl 150: 15-23.

Vieta E, Gasto C, Colom F, Reinares M, Martinez-Aran A, Benabarre A, Akiskal HS (2001) Role of risperidone in bipolar II: an open 6-month study. J Affect Disord 67: 213-219.

Wehr TA, Goodwin FK (1979) Rapid cycling in manic-depressives

induced by tricyclic antidepressants. Arch Gen Psychiatry 36: 555-559.

Whitlock FA, Evans LE (1978) Drugs and depression. Drugs 15: 53-71.

Yaroslavsky Y, Grisaru N, Chudakov B, Belmaker RH (1999) Is TMS therapeutic in mania as well as in depression? Electroencephalogr Clin Neurophysiol Suppl 51: 299-303.

Yatham LN (2000) Efficacy and tolerability of risperidone as combination therapy in bipolar mania: Results from a randomised, double-blind study (RIS-INT-46). Eur Neuropsychopharmacol 10 (Suppl 3): 250.