

Review

## Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder

Konstantinos N Fountoulakis\*<sup>1</sup>, Eduard Vieta<sup>2</sup>, Melina Siamouli<sup>1</sup>, Marc Valenti<sup>2</sup>, Stamatia Magiria<sup>1</sup>, Timucin Oral<sup>3</sup>, David Fresno<sup>2</sup>, Panteleimon Giannakopoulos<sup>4</sup> and George S Kaprinis<sup>1</sup>

Address: <sup>1</sup>Third Department of Psychiatry, Aristotle University of Thessaloniki, Greece, <sup>2</sup>Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain, <sup>3</sup>Fifth Inpatient Department of Psychiatry and Outpatient Unit of Mood Disorders, Bakirköy State Teaching and Research Hospital for Neuropsychiatry, Istanbul, Turkey and <sup>4</sup>Department of Psychiatry, University of Geneva, Switzerland

Email: Konstantinos N Fountoulakis\* - kfount@med.auth.gr; Eduard Vieta - evieta@clinic.ub.es; Melina Siamouli - siamel@msn.com; Marc Valenti - evieta@clinic.ub.es; Stamatia Magiria - routsonis@yahoo.com; Timucin Oral - etoral@superonline.com; David Fresno - evieta@clinic.ub.es; Panteleimon Giannakopoulos - Panteleimon.Giannakopoulos@medecine.unige.ch; George S Kaprinis - kaprinis@med.auth.gr

\* Corresponding author

Published: 9 October 2007

Received: 5 April 2007

*Annals of General Psychiatry* 2007, **6**:27 doi:10.1186/1744-859X-6-27

Accepted: 9 October 2007

This article is available from: <http://www.annals-general-psychiatry.com/content/6/1/27>

© 2007 Fountoulakis et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### Abstract

**Background:** Manic-depression or bipolar disorder (BD) is a multi-faceted illness with an inevitably complex treatment.

**Methods:** This article summarizes the current status of our knowledge and practice of its treatment.

**Results:** It is widely accepted that lithium is moderately useful during all phases of bipolar illness and it might possess a specific effectiveness on suicidal prevention. Both first and second generation antipsychotics are widely used and the FDA has approved olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole for the treatment of acute mania. These could also be useful in the treatment of bipolar depression, but only limited data exists so far to support the use of quetiapine monotherapy or the olanzapine-fluoxetine combination. Some, but not all, anticonvulsants possess a broad spectrum of effectiveness, including mixed dysphoric and rapid-cycling forms. Lamotrigine may be effective in the treatment of depression but not mania. Antidepressant use is controversial. Guidelines suggest their cautious use in combination with an antimanic agent, because they are supposed to induce switching to mania or hypomania, mixed episodes and rapid cycling.

**Conclusion:** The first-line psychosocial intervention in BD is psychoeducation, followed by cognitive-behavioral therapy. Other treatment options include Electroconvulsive therapy and transcranial magnetic stimulation. There is a gap between the evidence base, which comes mostly from monotherapy trials, and clinical practice, where complex treatment regimens are the rule.

## Background

The term 'bipolar disorder' (BD) is the contemporary label used for what is widely known as manic depressive illness, and was described for the first time by Hippocrates and Areteus. In modern times, Falret defined it as an illness in 1851. Today, two types are officially recognized, bipolar disorder type I and type II (BD-I and BD-II), and combined they account for a 3.7% prevalence rate or higher [1,2]. Both types constitute disabling conditions. Treatment aims to the resolution of symptoms, the restoration of psychosocial functioning and the prevention of relapses.

When collecting scientific data on the treatment of BD, diagnosis seems to be a problem as it is often retrospective and carries the risk of bias and memory distortions; hence it is of questionable reliability and validity.

Another problem is that while a specific treatment may be effective for the management of a specific cluster of symptoms, it may not be effective for the management of other clusters. Thus, treatment has to be regarded separately for each type of episode (manic, hypomanic, bipolar depression) and phase of the disease (acute, long-term and maintenance).

Double-blind, placebo-controlled studies are the main source of scientific proof of efficacy for available treatments. These should ideally be two-arm studies, including both the acute and the long-term (prophylactic or maintenance) phase, extending to a period of up to 6 or 12 months, depending on the investigated subtype. Nevertheless, there are no veracious data concerning all facets of affective illness.

The comparator agent is also an open issue, as it is still unclear whether this should be lithium, an antidepressant, an antipsychotic or something else, or whether the selection of the comparator agent should be based on the acute or the most recent phase. Likewise, it is still under consideration whether the ideal concept is that of a five-arm study, including a placebo and a drug-under-investigation group along with three comparator groups (lithium, antidepressant, antipsychotic). Such a concept of course is of very high financial cost, thus not yet used. The inclusion of a placebo group is of major importance [3], as its lack weakens the evidence; such a design cannot provide sufficiently accurate data because the underlying placebo response rate may be substantial and varies across, as well as within, studies. Furthermore, in the maintenance phase, the difference between placebo and an active comparator needs a follow-up period of at least 6 months, to be seen.

Another factor which may perplex the design of a clinical trial and the interpretation of its results is the fact that the patients' clinical condition and the natural history of the disease may be influenced by drug discontinuation, especially lithium discontinuation. This, especially when abrupt, is reported to elicit mania and lead to a refractory condition [4,5], thus affecting the results of a study. Age could be an additional confounding factor, as it may be responsible for an increased resistance to monotherapy [6].

Generalization of results is also a major problem. Treatments that are effective for unipolar depression are generally considered to be effective for bipolar depression as well, but not vice-versa [7]. Likewise, treatments that are effective for mania seem to be effective for hypomania as well, but not vice versa. However there is no sufficient data to support or reject these assumptions. As far as rapid cycling is concerned, data regarding the treatment of bipolar disorder in general do not necessarily apply to rapid cycling.

In this context, the development of treatment guidelines seems to be a rather important issue, in order to standardize treatment choices and apply research data to everyday clinical practice, by integrating information from different sources into easily applicable and accessible algorithms. The development of algorithms is mainly based on double-blind placebo-controlled trials, open studies and retrospective data analyses (experimental data). Expert opinion and clinical consensus is also taken under consideration, whereas consumer opinion may play an important role as well. Unlike earlier stages, which are simpler and more solidly evidence-based, as algorithms proceed to later stages, experimental data become ever more insufficient, resulting to a gradual take-over of expert opinion or clinical consensus.

Algorithms and guidelines facilitate clinical decision-making, reduce clinically inappropriate or cost-inefficient clinical practice decisions, and provide similar treatment across different settings but also a metric to assess patient response and a framework to evaluate the cost of treatment. Therefore they seem to be beneficial both for patients and the health system in general. Nevertheless, there are several potential problems associated with algorithms [8], e.g., disproportionate increase in cost-benefit ratio, biased consensus panel opinion, insufficient evidence for the development of an algorithm, poorer standard of care and inappropriate use due to a rigid, difficult to follow algorithm, suits for malpractice on the ground of deviation from an algorithm, etc.

The aim of this article is to summarize the contemporary knowledge and current practice concerning the treatment

of bipolar disorder, by performing a selective review of the literature.

### Existing treatment guidelines for bipolar disorder

To date, several papers about treatment guidelines for bipolar disorder have been published [8-40]. There are also a number of guideline documents developed by national bodies that have been published. The CANMAT [37] and the NICE [34] guidelines are the most recent, but even they fail to incorporate all recent findings and approvals [41].

The gradual acceptance of the use of atypical antipsychotics such as monotherapy and of antidepressants for a lim-

ited period of time, and in combination with antimanic agents, seems to be the trend [42]. A summary of guidelines is shown in Table 1.

### Lithium

It is generally accepted and supported by the literature that lithium is moderately useful against all phases of BD. It is also believed to exert a specific action on suicide prevention [36,43-50] and its use is strongly endorsed by all published treatment guidelines [42]. It seems to be a somewhat more effective against classic mania (the response rate being around 40%) than against depression [36,39,51,52]. It has a relatively slow onset of action; clin-

**Table 1: Guidelines for the treatment of bipolar disorder**

	Acute mania	Acute bipolar depression	Maintenance
TMAP, 2002	First step: Li, Vp, Olz Second step: Various combinations of two first choice agents	First step: Li, Vp, Olz, Li/Vp/Olz + SSRI/La Second step: Various combinations of two or more first choice agents, ECT	First step: Li, Vp, Olz, monotherapy or +AD (intermittent use) Second step: Various combinations of two or more first choice agents
WFSBP, 2003	First step: Li, Vp, Olz, Ris, Cbz Second step: Combinations of MS+aAPs, ECT	First step: AD+MS, SSRIs + Li/La/Vp/Cbz Second step: Combination of first choice agents, augmentation strategies, ECT	First step: After depression: AD+MS, SSRIs + Li/La/Vp/Cbz After mania: Li, MS, AP Second step: Combination of first choice agents
APA, 2002 and 2007	First step: Severe: Li/Vp+AP Mild-Moderate: Li, Vp, Olz Second step: Various combinations of two first choice agents, ECT 2007 update: Li for classic mania, Vp for mixed episodes, Cbz, Olz, Li/Vp+AP, ECT	First step: Li, La, Li+AD, ECT Second step: Various combinations of two first choice agents, ECT 2007 update: Li, Vp, La, MAOIs, SSRIs, Venf, TCAs, OFC, ECT	First step: Li, Vp, possibly Cbz, La, Ocbz. Continue the treatment proved efficient during the acute phase Second step: ECT, combination of first choice agents. AP should be discontinued 2007 update: Li, Vp, La, ECT
CANMAT, 2007	First step: Li, Vp, Olz, Ris, Quet, Arip, Zip, Li/Vp+Ris/Quet/Olz Second step: Cbz, Ocbz, ECT, Li+Vp Third step: Hal, Clpz, Li/Vp+Hal, Li+Cbz, Cloz	First step: Li, La, Li/Vp+SSRI, Olz+SSRI, Li/Vp+Bupr, Quet Second step: Quet+SSRI, Li/Vp+La Third step: 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	First step: Li, La, Vp, Olz Second step: Cbz, Li+Vp/Cbz, Li/Vp+Olz, Arip, Ris, Quet, Zip, Li+Ris/Quet, Li+La/SSRI/Bupr, OFC Third step: Adjunctive flupenthixol, gabapentin, topiramate, AD
NICE, 2006	First step: Severe: Olz, Quet, Ris. Li/Vp only in patients that previously responded to these agents. BZ if necessary Milder forms: Li/Vp Second step: Li/Vp+APP Third step: ECT	First step: SSRI+AM Second step: SSRI+Li/Vp+Quet, Mrz/Venf+AM Third step: ECT	First step: Discontinuation of Ads, keep Li/Olz/Vp Second step: Combinations of first step agents Third step: Combinations of first step agents plus La/Cbz

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; Quet, quetiapine; Ris, risperidone; SSRIs, Selective Serotonin Reuptake Inhibitors; TCA, Tricyclic antidepressant; Venf, venlafaxine; Vp, valproic; Zip, ziprasidone.

ical improvement generally occurs within 1 to 3 weeks of treatment.

A potential problem may be that after several years of successful use, a number of patients seem to develop a tolerance to lithium, while up to 15% of patients report a lithium discontinuation-induced refractoriness [53].

Resistance to lithium treatment could be predicted by the presence of mixed or dysphoric mania, rapid cycling, many prior episodes, poor interepisode functioning, an episode pattern of depression-mania-euthymia, comorbid substance abuse, and comorbid personality disorder [5,54]. By contrast, patients with an episodic course with euthymic intervals and the absence of rapid cycling may be better responders.

The recommended therapeutic Li blood levels for the treatment of acute mania range from 0.6–1.2 mEq/L, whereas maintenance levels could be lower, ranging from 0.6 to 0.9 mEq/L. Levels higher than 1.2 mEq/L are potentially toxic. When treating a patient with lithium, creatinine clearance is regarded to be the most reliable marker of kidney function to take into consideration.

Adverse events are to be expected during treatment with lithium [55], the most frequent being neurological, endocrinological (usually concerning the thyroid), cardiovascular, renal, gastrointestinal, hematological and dermatological manifestations and lithium intoxication. However, only about 30% of patients have more than minor complaints, whereas less than 20% of have no adverse effects at all.

#### **Anticonvulsants**

While lithium seems to be more specific to euphoric mania, specific anticonvulsants (but not all) seem to have a broad spectrum of effectiveness, including mixed, dysphoric and rapid-cycling forms.

Valproic acid is FDA approved for the treatment of acute manic episodes. Its response rate in acute mania is around 50%, compared to a placebo effect of 20–30% [48,54,56–63]. Patients respond relatively rapidly (within 1–2 weeks and often a few days). Valproate appears to have a more robust antimanic effect than lithium in rapid cycling and mixed episodes [63,64]. Concerning bipolar depression, there is only one controlled study supporting the effectiveness of valproate [57], whereas uncontrolled data suggest that it may be less effective than against mania (response rate close to 30%) [57,65]. Although valproate seems to have significant prophylactic antimanic properties, its prophylactic antidepressant ones are low-to-moderate [65–67]. Therapeutic serum levels range between 50 and 150 mg/mL. Gastrointestinal symptoms, sedation,

tremor, weight gain, hair loss, ataxia, dysarthria and persistent elevation of hepatic transaminases are among its common adverse effects.

Carbamazepine is approved by the FDA only for the treatment of bipolar mania. It is widely used, especially in continental Europe. The response rate against acute mania is close to 50% (similar to that of valproic) [68–71]. However, the response rate against bipolar depression appears to be lower (roughly 30% or less) [72,73]. Carbamazepine seems to be less effective in the prophylaxis against depressive than against manic/mixed episodes [69] and less effective than lithium [74–81]. The MAP study in 1997 [81,82] and a replication in 2003 [74] are the most important among studies comparing carbamazepine and lithium. Both studies showed a superiority of lithium over carbamazepine for the treatment of classic mania. A secondary analysis of the MAP data demonstrated that patients that don't respond to lithium may have a favourable response to carbamazepine [77], although its actual long-term efficacy is under question. The recommended dosage against acute mania is 600–1800 mg daily (blood concentration 4–12 mg/mL). Hepatic enzymes (CYP 3A4) induction occurs after several weeks, resulting to a lowering of drug levels. This may require additional upward dose titration [83]. Adverse effects are dose-related and include double or blurred vision, dizziness, sedation, ataxia, and diplopia, vertigo, gastrointestinal disturbances, cognitive impairment and hematological effects [5,84,85]. The induction of the metabolism of antidepressants, antipsychotics and other anticonvulsants is yet another major problem which makes the use of carbamazepine during combination treatment problematic.

Lamotrigine, at a daily dosage of 50–200 mg may be effective in the treatment of acute bipolar depression but not mania [45,86–93]. Moreover, it may be equally effective to lithium in the prophylaxis of any mood episode [22,45]. In depression, response rates are double than those observed under placebo (close to 50%). Lamotrigine may also be effective against rapid cycling [54]. Treatment should be initiated slowly; 25 mg daily for the first 2 weeks and then 50 mg for another 2 weeks, followed by slow increases, in order to avoid a moderately high incidence of rash.

Topiramate and gabapentin can only be used as supplementary therapy for the treatment of weight gain (topiramate) and anxiety (gabapentin), as data on them is negative [94–97]. Data regarding other anticonvulsants is not reliable. It must be pointed out that unlike antipsychotics, that seem to have a possibly antidopaminergic 'class effect' limited to the treatment of acute mania, anticonvulsants have no such effect in any phase of bipolar

disorder. Each agent has a very distinct pharmacologic profile, thus should be considered separately.

### **Antipsychotics**

First generation (typical) antipsychotics (FGAs) are considered to be the traditional first-line treatment for acute mania, especially in Europe. TGAs, mostly haloperidol, have been used for long and are generally regarded to act faster than mood stabilizers. Nevertheless, many psychiatrists share the anecdotal clinical impression that FGAs induce depression.

Unlike FGAs, second generation (atypical) antipsychotics (SGAs) do not induce depression. Moreover, several recent studies support their usefulness in all phases of bipolar illness, either as monotherapy or as an adjunct to conventional mood stabilizers. They have a lower incidence of extrapyramidal symptoms and signs, thus considered to have a more favourable adverse effects profile. Improvement is reported to be similar among different antipsychotic agents, irrespective of whether the antipsychotic was utilized as monotherapy or adjunctive therapy [98]. Olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have already been approved by the FDA for the treatment of acute mania. These drugs are also approved for the treatment of mania in most European countries. Although available data is still limited, SGAs are considered a rather promising option for treating bipolar depression.

The use of adjunct SGAs on anticonvulsants produces a response rate increase of about 20%, while, when used as monotherapy, SGAs produce a roughly 20% difference from placebo.

Risperidone effectiveness in acute mania is supported in several studies [99] with remission rates of 42% vs 13% for placebo [85,100-107]. Dose-related extrapyramidal symptoms, weight gain, sedation and hyperprolactinemia seem to be its main disadvantages [99]. There are also a number of studies that included patients with mixed states [101,102,106].

Olanzapine has the highest number of published randomized control trials (RCTs) [1,60,85,87,108-128] and a solid basis supporting its use in bipolar disorder [129], hence it is the most well-studied atypical antipsychotic. It is approved by the FDA, but not the EMEA, for the treatment of bipolar depression (only in combination with fluoxetine), and for the maintenance phase for those patients that responded well to olanzapine during an acute manic episode [118,122,130]. Regarding mixed episodes, there are some available data, however its use is not well established. The most common adverse effects

reported include dry mouth, weight gain, increased appetite and somnolence [60].

Quetiapine effectiveness in both mania and depression as monotherapy is supported by RCTs [59,69,131-139]. It is currently the only SGA approved by the FDA as a monotherapy (300–600 mg/daily) for both acute mania and bipolar depression. In depression trials, 600 mg/day were found not to be more effective than 300 mg/day. Concerning mixed episodes and rapid cycling, only some uncontrolled data is available [21,135]. The most common adverse effects include somnolence and hypotension.

The use of aripiprazole and ziprasidone as monotherapy in manic or mixed episodes is supported by existing data [42,140-144]. The most common adverse events are akathisia (Aripiprazole), somnolence and extrapyramidal symptoms (Ziprasidone).

### **Antidepressants**

Currently, fluoxetine, as part of the fluoxetine plus olanzapine combination, is the only antidepressant medication officially approved by the FDA for the treatment of bipolar depression [87,112,126].

In spite of the fact that there are some double-blind studies supporting their effectiveness against bipolar depression [145-147], this is still an open issue. Thus, their use and usefulness in bipolar disorder is still controversial [102]. Guidelines suggest their cautious use, always in combination with an antimanic agent [139], as antidepressants may induce switching to mania or hypomania, mixed episodes and rapid cycling [148-151]. In patients receiving a mood stabilizer, the outcome of depression could be improved by the addition of an antidepressant without significantly altering the risk of switch [152]. According to earlier studies, switching to mania or hypomania was a considerable risk, especially with tricyclics [46,153]. However, this may not apply to newer agents. Switching to mania or hypomania may occur in 7–30% of patients. This depends on the antidepressant agent and dose used and the personal (prepubertal onset) and family history [154,155]. Nevertheless, it is supported by some authors that the true rate of switching is rather low, if any [154,156-158]. The general concept however, is that dual action agents (TCAs or Serotonin and Noradrenaline Reuptake Inhibitors – SNRIs) may be more potent in increasing the risk for switching to mania or hypomania [148,159] and to development of suicidal ideation [38,160,161]. An adjunctive antimanic agent (atypical antipsychotic or anticonvulsant) may protect against switching or mixed symptoms, but this is not always the case [148,162].

A warning regarding the possible induction of suicidality (ideas and behavior but not completed suicide) by antidepressants in children and adolescents and possibly in all age groups, has been recently issued by the FDA [163], however data from the STEP-BD program does not support the idea of increased suicidality in bipolar patients treated with antidepressants [164]. Thus, this issue remains controversial.

#### **Psychotherapy and other non-pharmacological therapies**

Hard data concerning the effectiveness of psychosocial interventions in BD are emerging. Psychoeducation is what appears to be the first line of psychosocial intervention. In bipolar patients under medication, psychoeducation, family-focused psychoeducation and cognitive-behavioral therapy seem to be the most efficacious interventions for relapse prevention. Moreover, they can help both the patient and family members to learn to recognize early warning signs of oncoming episodes, thus obtain earlier treatment interventions, and to identify possible triggering factors [165].

Although there are no definite data, the efficacy of electroconvulsive therapy (ECT) in acute mania is supported by several older clinical observations and some more recent clinical trials [166-168]. 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 [169-171].

#### **Discussion**

Previously, there has been an obvious discrepancy between recommendations made by opinion leaders and researchers and decisions made by clinicians in everyday practice. This discrepancy appeared to depict the different approaches to bipolar disorder in US and Europe, and, although today it is significantly smaller, somehow it still exists.

Treatment guidelines strongly emphasize monotherapy during the first stage of treatment algorithms. However, reality proves that this first stage is practically useless or that clinicians do not seem to appreciate it. Statistics show that the vast majority of BD patients receive more than one medication, with a significant percentage receiving three or more. Only 5–10% of patients are on monotherapy, whereas half may receive at least three different agents [172,173]. Therefore, recently, combination therapy is gaining ground even in treatment guidelines [36].

A comprehensive evaluation of the data concerning the various treatment modalities against the different facets of BD is shown in Table 2. The literature suggests that proper treatment of BD patients needs continuous administration of an antimanic agent [42], but this may be one of the

**Table 2: Grading of data on the basis of a modified POST method**

Agent/modality	Acute mania	Acute bipolar depression	Maintenance treatment
Amisulpride	+	ND	+
Aripiprazole	++++	-	+++
Benzodiazepines	+	ND	ND
Carbamazepine	++++	++	+++
Citalopram	ND	+	+
Clozapine	++	ND	++
ECT	++	+++	+
Fluoxetine	ND	++++	++
Gabapentin	-	-	++
Lamotrigine	-	++++	++++
Lithium	++++	++++	++++
Olanzapine	++++	+++	++++
Olanzapine-fluoxetine combination	ND	++++	++
Quetiapine	++++	++++	ND
Risperidone	++++	ND	ND
Topiramate	-	+	ND
Valproiate	++++	+++	+++
Ziprasidone	++++	ND	ND
Psychoeducation	ND	ND	++++
TMS	ND	ND	ND

++++, good research-based evidence, supported randomized placebo-controlled and comparison trials; +++, fair research-based evidence, supported by randomized controlled trials but there are some drawbacks (small sample size or no placebo control); ++, some evidence on the basis of at least one small scale RCT; +, Recommendation based on prospective case studies, or large scale retrospective chart analyses and support by expert opinion; -, negative data; ND, no data.

reasons why depression predominates in the course of bipolar disorder.

Against acute mania, SGAs might act faster and better than lithium and anticonvulsants while their efficacy during the maintenance phase may be comparable. Quetiapine and the olanzapine plus fluoxetine combination have proven efficacy against both mania and bipolar depression. An SGA alone could be enough to control the disease manifestations in patients with a history of predominant manic or mixed episodes and rare and short depressive episodes [174]. Adding lamotrigine and increase it slowly up to 200 mg daily could help in controlling depressive symptoms. Antidepressants (mainly SSRIs), if needed, should be initiated at a low dosage with careful titration [34]. Other options for treatment-resistant patients include MAOIs, and ECT. Some authors suggest that after the second episode of bipolar illness, long term treatment is necessary and it has been claimed that maintenance treatment should last at least 2 years after an episode or 5 years if the patient has risk factors for relapse [34], however in clinical practice it is better to plan for lifetime treatment unless contraindications or specific issues argue against it.

### Competing interests

The author(s) declare that they have no competing interests.

### Acknowledgements

KNF has received honoraria for lectures from Astra-Zeneca, Janssen-Cilag, Eli-Lilly and a research grant from Pfizer Foundation. EV has acted as consultant, received grants, or received honoraria for lectures from the following companies: Ammiral, Astra-Zeneca, Bial, Bristol-Myers-Squibb, Eli-Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Lundbeck, Merck-Sharp-Dohme, Novartis, Organon, Pfizer, Sanofi, Servier, UCB.

### References

- Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW: **The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder.** *J Clin Psychiatry* 2003, **64(7)**:841-846.
- Angst J: **The emerging epidemiology of hypomania and bipolar II disorder.** *Journal of Affective Disorders* 1998, **50**:143-151.
- Vieta E, Carne X: **The use of placebo in clinical trials on bipolar disorder: a new approach for an old debate.** *Psychother Psychosom* 2005, **74(1)**:10-16.
- Suppes T, Baldessarini RJ, Faedda GL, Tohen M: **Risk of recurrence following discontinuation of lithium treatment in bipolar disorder.** *Archives of General Psychiatry* 1991, **48**:1082-1088.
- Faedda GL, Baldessarini RJ, Tohen M, Strakowski SM, Waternaux C: **Episode sequence in bipolar disorder and response to lithium treatment.** *Am J Psychiatry* 1991, **148(9)**:1237-1239.
- Maj M, Priozzi R, Kemali D: **Long-term outcome of lithium prophylaxis in patients initially classified as complete responders.** *Psychopharmacology (Berl)* 1988, **98(4)**:535-538.
- Cohn JB, Collins G, Ashbrook E, Wernicke JF: **A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder.** *Int Clin Psychopharmacol* 1989, **4(4)**:313-322.
- Rush AJ, Rago WV, Crismon ML, Toprac MG, Shon SP, Suppes T, Miller AL, Trivedi MH, Swann AC, Biggs MM, Shores-Wilson K, Kashner TM, Pigott T, Chiles JA, Gilbert DA, Altshuler KZ: **Medication treatment for the severely and persistently mentally ill: the Texas Medication Algorithm Project.** *J Clin Psychiatry* 1999, **60(5)**:284-291.
- Expert consensus guidelines are released for the treatment of bipolar disorder. **Consensus Development Conferences.** *Am Fam Physician* 1997, **55(4)**:1447-1449.
- AACAP: **AACAP official action. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder.** *J Am Acad Child Adolesc Psychiatry* 1997, **36(1)**:138-157.
- Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP: **The Expert Consensus Guideline Series. Treatment of behavioral emergencies.** *Postgrad Med* 2001:1-88; quiz 89-90.
- APA: **Practice guideline for the treatment of patients with bipolar disorder.** **American Psychiatric Association.** *Am J Psychiatry* 1994, **151(12 Suppl)**:1-36.
- APA: **American Psychiatric Association releases treatment guideline for bipolar disease.** *Am Fam Physician* 1995, **51(6)**:1605-1606.
- American Psychiatric Association: **Practice guideline for the treatment of patients with bipolar disorder (revision).** *Am J Psychiatry* 2002, **159(4 Suppl)**:1-50.
- Barreira P, Duckworth K, Goff D, Flannery RB Jr.: **Clinical practice guidelines: the Massachusetts experience in psychiatry.** *Harv Rev Psychiatry* 1999, **7(4)**:230-232.
- Gilbert DA, Altshuler KZ, Rago WV, Shon SP, Crismon ML, Toprac MG, Rush AJ: **Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms.** *J Clin Psychiatry* 1998, **59(7)**:345-351.
- Dennehy EB: **Guidelines for treatment of bipolar disorder.** *Curr Psychiatry Rep* 2000, **2(4)**:316-321.
- Goldberg JF: **Treatment guidelines: current and future management of bipolar disorder.** *J Clin Psychiatry* 2000, **61 Suppl** 13:12-18.
- Goodwin GM, Bourgeois MI, Conti L: **Treatment of bipolar depressive mood disorders: algorithms for pharmacotherapy.** *Int J Psychiatry Clin Pract* 1997, **1**:S9-S12.
- Goodwin GM: **Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology.** *J Psychopharmacol* 2003, **17(2)**:149-73; discussion 147.
- Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, Vieta E, Moller HJ: **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* 2002, **3(3)**:115-124.
- Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, Vieta E, Moller HJ: **The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania.** *World J Biol Psychiatry* 2003, **4(1)**:5-13.
- Jobson K: **International Psychopharmacology Algorithm Project: Algorithms in psychopharmacology.** *Int J Psychiatry Clin Pract* 1997, **1**:S3-S8.
- Kusumakar V, Yatham LN, Parikh SV: **Bipolar disorder: a summary of clinical issues and treatment options.** Halifax, Nova Scotia: CANMAT Monograph ; 1997.
- Licht RW, Vestergaard P, Kessing LV, Larsen JK, Thomsen PH, Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark: **Psychopharmacological treatment with lithium and antiepileptic drugs: suggested guidelines from the Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark.** *Acta Psychiatr Scand Suppl* 2003, **419**:1-22.
- McClellan J, Werry J: **Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder.** **American Academy of Child and Adolescent Psychiatry.** *J Am Acad Child Adolesc Psychiatry* 1997, **36(10 Suppl)**:157S-76S.
- Montgomery DB: **ECNP Consensus Meeting March 2000 Nice: guidelines for investigating efficacy in bipolar disorder.** **European College of Neuropsychopharmacology.** *Eur Neuropsychopharmacol* 2001, **11(1)**:79-88.
- Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Trivedi MH, Suppes T, Miller AL, Biggs MM, Shores-Wilson K, Witte BP, Shon SP, Rago WV, Altshuler KZ: **Texas Medication Algorithm**

- Project, phase 3 (TMAP-3): rationale and study design.** *J Clin Psychiatry* 2003, **64(4)**:357-369.
29. Sachs GS, Prinz DJ, Kahn DA, Carpenter D, Docherty JP: **The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000.** *Postgrad Med* 2000, **Spec No**:1-104.
  30. Suppes T, Calabrese JR, Mitchell PB, Pazzaglia PJ, Potter WZ, Zarlin DA: **Algorithms for the treatment of bipolar manic-depressive illness.** *Psychopharmacol Bull* 1995, **31(3)**:469-474.
  31. Suppes T, Dennehy EB, Swann AC, Bowden CL, Calabrese JR, Hirschfeld RM, Keck PE Jr., Sachs GS, Crismon ML, Toprac MG, Shon SP: **Report of the Texas Consensus Conference Panel on medication treatment of bipolar disorder 2000.** *J Clin Psychiatry* 2002, **63(4)**:288-299.
  32. Suppes T, Rush AJ, Dennehy EB, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Brown ES, Biggs MM, Shores-Wilson K, Witte BP, Trivedi MH, Miller AL, Altshuler KZ, Shon SP: **Texas Medication Algorithm Project, phase 3 (TMAP-3): clinical results for patients with a history of mania.** *J Clin Psychiatry* 2003, **64(4)**:370-382.
  33. Suppes T, Swann AC, Dennehy EB, Habermacher ED, Mason M, Crismon ML, Toprac MG, Rush AJ, Shon SP, Altshuler KZ: **Texas Medication Algorithm Project: development and feasibility testing of a treatment algorithm for patients with bipolar disorder.** *J Clin Psychiatry* 2001, **62(6)**:439-447.
  34. O'Dowd A: **NICE issues new guidance to improve the treatment of bipolar disorder.** *Bmj* 2006, **333(7561)**:220.
  35. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, Sharma V, Silverstone P, Alda M, Baruch P, Beaulieu S, Daigneault A, Milev R, Young LT, Ravindran A, Schaffer A, Connolly M, Gorman CP: **Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies.** *Bipolar Disord* 2005, **7 Suppl 3**:5-69.
  36. Grunze H, Kasper S, Goodwin G, Bowden C, Moller HJ: **The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment.** *World J Biol Psychiatry* 2004, **5(3)**:120-135.
  37. Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, Sharma V, Beaulieu S: **Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007.** *Bipolar Disord* 2006, **8(6)**:721-739.
  38. Frances AJ, Docherty JP, Kahn DA: **The Expert Consensus Guideline Series: Treatment of Bipolar Disorder.** *J Clin Psychiatry* 1996, **57(suppl12A)**:1-88.
  39. Bauer MS, Callahan AM, Jampala C, Petty F, Sajatovic M, Schaefer V, Wittlin B, Powell BJ: **Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs.** *J Clin Psychiatry* 1999, **60(1)**:9-21.
  40. Hirschfeld RMA: **Guideline Watch for the Practice Guideline for the Treatment of Patients With Bipolar Disorder.** Arlington, VA, American Psychiatric Association; 2005.
  41. Vieta E, Nolen WA, Grunze H, Licht RW, Goodwin G: **A European perspective on the Canadian guidelines for bipolar disorder.** *Bipolar Disord* 2005, **7 Suppl 3**:73-76.
  42. Fountoulakis KN, Vieta E, Sanchez-Moreno J, Kaprinis SG, Goikolea JM, Kaprinis GS: **Treatment guidelines for bipolar disorder: a critical review.** *J Affect Disord* 2005, **86(1)**:1-10.
  43. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM: **Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials.** *Am J Psychiatry* 2004, **161(2)**:217-222.
  44. Baldessarini RJ, Tondo L, Hennen J: **Lithium treatment and suicide risk in major affective disorders: update and new findings.** *J Clin Psychiatry* 2003, **64 Suppl 5**:44-52.
  45. Calabrese JR, Goldberg JF, Ketter TA, Suppes T, Frye M, White R, DeVeaugh-Geiss A, Thompson TR: **Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies.** *Biol Psychiatry* 2006, **59(11)**:1061-1064.
  46. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: **Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination.** *Arch Gen Psychiatry* 1984, **41(11)**:1096-1104.
  47. Kane JM, Quitkin FM, Rifkin A, Ramos-Loreni JR, Nayak DD, Howard A: **Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison.** *Arch Gen Psychiatry* 1982, **39(9)**:1065-1069.
  48. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsaver SC, Davis JM, Rush AJ, Small JG: **Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group.** *JAMA* 1994, **271(12)**:918-924.
  49. Kessing LV, Sondergard L, Kvist K, Andersen PK: **Suicide risk in patients treated with lithium.** *Arch Gen Psychiatry* 2005, **62(8)**:860-866.
  50. Cipriani A, Pretty H, Hawton K, Geddes JR: **Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials.** *Am J Psychiatry* 2005, **162(10)**:1805-1819.
  51. Calabrese JR, Vieta E, Shelton MD: **Latest maintenance data on lamotrigine in bipolar disorder.** *Eur Neuropsychopharmacol* 2003, **13 Suppl 2**:S57-66.
  52. Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM: **Spotlight on lamotrigine in bipolar disorder.** *CNS Drugs* 2004, **18(1)**:63-67.
  53. Post RM, Leverich GS, Altshuler L, Mikalaukas K: **Lithium-discontinuation-induced refractoriness: Preliminary observations.** *Am J Psychiatry* 1992, **149**:1727.
  54. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG Jr., Chou JC, Keck PE Jr., Rhodes LJ, Swann AC, Hirschfeld RM, Wozniak PJ: **A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group.** *Arch Gen Psychiatry* 2000, **57(5)**:481-489.
  55. Silverstone PH, Bell EC, Willson MC, Dave S, Wilman AH: **Lithium alters brain activation in bipolar disorder in a task- and state-dependent manner: an fMRI study.** *Ann Gen Psychiatry* 2005, **4**:14.
  56. Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL: **A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder.** *Am J Psychiatry* 2005, **162(11)**:2152-2161.
  57. Davis LL, Bartolucci A, Petty F: **Divalproex in the treatment of bipolar depression: a placebo-controlled study.** *J Affect Disord* 2005, **85(3)**:259-266.
  58. Pope HG Jr., McElroy SL, Keck PE Jr., Hudson JI: **Valproate in the treatment of acute mania. A placebo-controlled study.** *Arch Gen Psychiatry* 1991, **48(1)**:62-68.
  59. Sachs G, Chengappa KN, Suppes T, Mullen JA, Brecher M, Devine NA, Sweitzer DE: **Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study.** *Bipolar Disord* 2004, **6(3)**:213-223.
  60. Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, Milton DR, Risser R, Gilmore JA, Breier A, Tollefson GA: **Olanzapine versus divalproex in the treatment of acute mania.** *Am J Psychiatry* 2002, **159(6)**:1011-1017.
  61. Welge JA, Keck PE Jr., Meinhold JM: **Predictors of response to treatment of acute bipolar manic episodes with divalproex sodium or placebo in 2 randomized, controlled, parallel-group trials.** *J Clin Psychopharmacol* 2004, **24(6)**:607-612.
  62. Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA, Abi-Saab W, Saltarelli M: **A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania.** *J Clin Psychiatry* 2006, **67(10)**:1501-1510.
  63. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC: **A double-blind comparison of valproate and lithium in the treatment of acute mania.** *Am J Psychiatry* 1992, **149(1)**:108-111.
  64. Calabrese JR, Woyshville MJ, Kimmel SE, Rapport DJ: **Predictors of valproate response in bipolar rapid cycling.** *J Clin Psychopharmacol* 1993, **13(4)**:280-283.
  65. Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, Chou JC, Wassef A, Risch CS, Hirschfeld RM, Nemeroff CB, Keck PE Jr., Evans DL, Wozniak PJ: **Maintenance efficacy of divalproex in the prevention of bipolar depression.** *Neuropsychopharmacology* 2003, **28(7)**:1374-1382.



66. Puzynski S, Klosiewicz L: **Valproic acid amide in the treatment of affective and schizoaffective disorders.** *J Affect Disord* 1984, **6(1)**:115-121.
67. Solomon DA, Ryan CE, Keitner GI, Miller IW, Shea MT, Kazim A, Keller MB: **A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder.** *J Clin Psychiatry* 1997, **58(3)**:95-99.
68. Lerer B, Moore N, Meyendorff E, Cho SR, Gershon S: **Carbamazepine versus lithium in mania: a double-blind study.** *J Clin Psychiatry* 1987, **48(3)**:89-93.
69. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR: **Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study).** *J Clin Psychopharmacol* 2006, **26(6)**:600-609.
70. Weisler RH, Kalali AH, Ketter TA: **A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes.** *J Clin Psychiatry* 2004, **65(4)**:478-484.
71. Owen RT: **Extended-release carbamazepine for acute bipolar mania: a review.** *Drugs Today (Barc)* 2006, **42(5)**:283-289.
72. Ballenger JC, Post RM: **Carbamazepine in manic-depressive illness: a new treatment.** *Am J Psychiatry* 1980, **137(7)**:782-790.
73. Post RM, Uhde TW, Roy-Byrne PP, Joffe RT: **Antidepressant effects of carbamazepine.** *Am J Psychiatry* 1986, **143(1)**:29-34.
74. Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA: **Prophylactic efficacy of lithium versus carbamazepine in treatment-naïve bipolar patients.** *J Clin Psychiatry* 2003, **64(2)**:144-151.
75. Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM: **Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder.** *J Clin Psychiatry* 1997, **58(11)**:470-478.
76. Fritze J, Beneke M, Lanczik M, Schneider B, Walden J: **Carbamazepine as adjunct or alternative to lithium in the prophylaxis of recurrent affective disorders.** *Pharmacopsychiatry* 1994, **27**:181.
77. Greil W, Kleindienst N, Erazo N, Muller-Oerlinghausen B: **Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder.** *J Clin Psychopharmacol* 1998, **18**:455.
78. Coxhead N, Silverstone T, Cookson J: **Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder.** *Acta Psychiatr Scand* 1992, **85(2)**:114-118.
79. Post RM, Uhde TW, Ballenger JC, Squillace KM: **Prophylactic efficacy of carbamazepine in manic-depressive illness.** *Am J Psychiatry* 1983, **140(12)**:1602-1604.
80. Watkins SE, Callender K, Thomas DR, Tidmarsh SF, Shaw DM: **The effect of carbamazepine and lithium on remission from affective illness.** *Br J Psychiatry* 1987, **150**:180-182.
81. Greil W, Ludwig-Mayerhofer W, Erazo N, Schochlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Muller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: **Lithium versus carbamazepine in the maintenance treatment of bipolar disorders--a randomised study.** *J Affect Disord* 1997, **43(2)**:151-161.
82. Kleindienst N, Greil W: **Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study.** *Neuropsychobiology* 2000, **42 Suppl 1**:2-10.
83. Bertilsson L, Tomson T: **Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine 10,11-epoxide: An update.** *Clin Pharmacokinet* 1986, **11**:177.
84. Blackburn SC, Oliart AD, Garcia Rodriguez LA, Perez Gutthann S: **Antiepileptics and blood dyscrasias: A cohort study.** *Pharmacotherapy* 1998, **18**:1277.
85. Perlis RH, Baker RW, Zarate CA Jr., Brown EB, Schuh LM, Jamal HH, Tohen M: **Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial.** *J Clin Psychiatry* 2006, **67(11)**:1747-1753.
86. Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hombland M, Montgomery P, Earl N, Smoot TM, DeVaugh-Geiss J: **A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.** *Arch Gen Psychiatry* 2003, **60(4)**:392-400.
87. Brown EB, McElroy SL, Keck PE Jr., Deldar A, Adams DH, Tohen M, Williamson DJ: **A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression.** *J Clin Psychiatry* 2006, **67(7)**:1025-1033.
88. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVaugh-Geiss J: **A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder.** *J Clin Psychiatry* 2003, **64(9)**:1013-1024.
89. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD: **A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group.** *J Clin Psychiatry* 1999, **60(2)**:79-88.
90. Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, Kusumakar V, Ascher JA, Earl NL, Greene PL, Monaghan ET: **A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group.** *J Clin Psychiatry* 2000, **61(11)**:841-850.
91. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R: **A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder.** *J Clin Psychiatry* 2004, **65(3)**:432-441.
92. Ichim L, Berk M, Brook S: **Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial.** *Ann Clin Psychiatry* 2000, **12(1)**:5-10.
93. McElroy SL, Zarate CA, Cookson J, Suppes T, Huffman RF, Greene P, Ascher J: **A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression.** *J Clin Psychiatry* 2004, **65(2)**:204-210.
94. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G: **Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group.** *Bipolar Disord* 2000, **2(3 Pt 2)**:249-255.
95. Vieta E, Manuel Goikolea J, Martinez-Aran A, Comes M, Verger K, Masramon X, Sanchez-Moreno J, Colom F: **A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder.** *J Clin Psychiatry* 2006, **67(3)**:473-477.
96. Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA: **Gabapentin augmentation therapy in bipolar depression.** *Bipolar Disord* 2002, **4(5)**:296-301.
97. Kushner SF, Khan A, Lane R, Olson WH: **Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials.** *Bipolar Disord* 2006, **8(1)**:15-27.
98. Perlis RH, Welge JA, Vornik LA, Hirschfeld RM, Keck PE Jr.: **Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials.** *J Clin Psychiatry* 2006, **67(4)**:509-516.
99. Rendell JM, Gijsman HJ, Bauer MS, Goodwin GM, Geddes GR: **Risperidone alone or in combination for acute mania.** *Cochrane Database Syst Rev* 2006:CD004043.
100. Gopal S, Steffens DC, Kramer ML, Olsen MK: **Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy.** *J Clin Psychiatry* 2005, **66(8)**:1016-1020.
101. Hirschfeld RM, Keck PE Jr., Kramer M, Karcher K, Canuso C, Eerdeken M, Grossman F: **Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial.** *Am J Psychiatry* 2004, **161(6)**:1057-1065.
102. Khanna S, Vieta E, Lyons B, Grossman F, Eerdeken M, Kramer M: **Risperidone in the treatment of acute mania: double-blind, placebo-controlled study.** *Br J Psychiatry* 2005, **187**:229-234.
103. Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, Miyahara S, Bauer MS, Thase ME, Wisniewski SR, Sachs GS: **Treatment-resistant bipolar depression: a STEP-BD equipose randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone.** *Am J Psychiatry* 2006, **163(2)**:210-216.
104. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL: **Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety.** *Am J Psychiatry* 2002, **159(7)**:1146-1154.

105. Segal J, Berk M, Brook S: **Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial.** *Clin Neuropharmacol* 1998, **21(3)**:176-180.
106. Smulevich AB, Khanna S, Eerdeken M, Karcher K, Kramer M, Grossman F: **Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol.** *Eur Neuropsychopharmacol* 2005, **15(1)**:75-84.
107. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A: **Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial.** *Br J Psychiatry* 2003, **182**:141-147.
108. Baker RW, Tohen M, Fawcett J, Risser RC, Schuh LM, Brown E, Stauffer VL, Shao L, Tollefson GD: **Acute dysphoric mania: treatment response to olanzapine versus placebo.** *J Clin Psychopharmacol* 2003, **23(2)**:132-137.
109. Baldessarini RJ, Hennen J, Wilson M, Calabrese J, Chengappa R, Keck PE Jr., McElroy SL, Sachs G, Vieta E, Welge JA, Yatham LN, Zarate CA Jr., Baker RW, Tohen M: **Olanzapine versus placebo in acute mania: treatment responses in subgroups.** *J Clin Psychopharmacol* 2003, **23(4)**:370-376.
110. Berk M, Ichim L, Brook S: **Olanzapine compared to lithium in mania: a double-blind randomized controlled trial.** *Int Clin Psychopharmacol* 1999, **14(6)**:339-343.
111. Chengappa KN, Baker RW, Shao L, Yatham LN, Tohen M, Gershon S, Kupfer DJ: **Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania.** *Bipolar Disord* 2003, **5(1)**:1-5.
112. Corya SA, Perlis RH, Keck PE Jr., Lin DY, Case MG, Williamson DJ, Tohen MF: **A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression.** *J Clin Psychiatry* 2006, **67(5)**:798-806.
113. Houston JP, Ahl J, Meyers AL, Kaiser CJ, Tohen M, Baldessarini RJ: **Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex.** *J Clin Psychiatry* 2006, **67(8)**:1246-1252.
114. Houston JP, Lipkovich IA, Ahl J, Rotelli MD, Baker RW, Bowden CL: **Initial symptoms of manic relapse in manic or mixed-manic bipolar disorder: Post hoc analysis of patients treated with olanzapine or lithium.** *J Psychiatr Res* 2005.
115. Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, Koch M, Rizk R, Walker D, Tran P, Breier A: **A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania.** *J Clin Psychopharmacol* 2001, **21(4)**:389-397.
116. Shi L, Namjoshi MA, Swindle R, Yu X, Risser R, Baker RW, Tohen M: **Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial.** *Clin Ther* 2004, **26(1)**:125-134.
117. Suppes T, Brown E, Schuh LM, Baker RW, Tohen M: **Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data.** *J Affect Disord* 2005, **89(1-3)**:69-77.
118. Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, Baker RW, Chou JC, Bowden CL: **Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine.** *Am J Psychiatry* 2006, **163(2)**:247-256.
119. Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, Sachs GS, Kupfer DJ, Ghaemi SN, Feldman PD, Risser RC, Evans AR, Calabrese JR: **Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone.** *Br J Psychiatry* 2004, **184**:337-345.
120. Tohen M, Chengappa KN, Suppes T, Zarate CA Jr., Calabrese JR, Bowden CL, Sachs GS, Kupfer DJ, Baker RW, Risser RC, Keeter EL, Feldman PD, Tollefson GD, Breier A: **Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy.** *Arch Gen Psychiatry* 2002, **59(1)**:62-69.
121. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, Azorin JM, Vieta E, Hardy-Bayle MC, Lawson VB, Emsley RA, Zhang F, Baker RW, Risser RC, Namjoshi MA, Evans AR, Breier A: **A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania.** *Arch Gen Psychiatry* 2003, **60(12)**:1218-1226.
122. Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, Koukopoulos A, Cassano GB, Grunze H, Licht RW, Dell'Osso L, Evans AR, Risser R, Baker RW, Crane H, Dossenbach MR, Bowden CL: **Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial.** *Am J Psychiatry* 2005, **162(7)**:1281-1290.
123. 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: **Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group.** *Arch Gen Psychiatry* 2000, **57(9)**:841-849.
124. Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altschuler L, Zajecka J, Schuh LM, Risser RC, Brown E, Baker RW: **Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study.** *Am J Psychiatry* 2003, **160(7)**:1263-1271.
125. 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: **Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group.** *Am J Psychiatry* 1999, **156(5)**:702-709.
126. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A: **Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression.** *Arch Gen Psychiatry* 2003, **60(11)**:1079-1088.
127. Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW: **A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder.** *J Clin Psychiatry* 2002, **63(12)**:1148-1155.
128. Zhu B, Tunis SL, Zhao Z, Baker RW, Lage MJ, Shi L, Tohen M: **Service utilization and costs of olanzapine versus divalproex treatment for acute mania: results from a randomized, 47-week clinical trial.** *Curr Med Res Opin* 2005, **21(4)**:555-564.
129. Rendell JM, Gijnsman HJ, Keck P, Goodwin GM, Geddes JR: **Olanzapine alone or in combination for acute mania.** *Cochrane Database Syst Rev* 2003:CD004040.
130. Ketter TA, Houston JP, Adams DH, Risser RC, Meyers AL, Williamson DJ, Tohen M: **Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes.** *J Clin Psychiatry* 2006, **67(1)**:95-101.
131. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vagero M, Svensson K: **A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder.** *J Clin Psychiatry* 2005, **66(1)**:111-121.
132. Calabrese JR, Keck PE Jr., Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J: **A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression.** *Am J Psychiatry* 2005, **162(7)**:1351-1360.
133. Cookson J, Keck PE Jr., Ketter TA, Macfadden W: **Number needed to treat and time to response/remission for quetiapine monotherapy efficacy in acute bipolar depression: evidence from a large, randomized, placebo-controlled study.** *Int Clin Psychopharmacol* 2007, **22(2)**:93-100.
134. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, Nelson E, Strakowski SM: **A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania.** *J Am Acad Child Adolesc Psychiatry* 2006, **45(3)**:305-313.
135. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM: **A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania.** *J Am Acad Child Adolesc Psychiatry* 2002, **41(10)**:1216-1223.
136. Endicott J, Rajagopalan K, Minkwitz M, Macfadden W: **A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life.** *Int Clin Psychopharmacol* 2007, **22(1)**:29-37.

137. McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J: **Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial.** *Eur Neuropsychopharmacol* 2005, **15(5)**:573-585.
138. Vieta E, Mullen J, Brecher M, Paulsson B, Jones M: **Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies.** *Curr Med Res Opin* 2005, **21(6)**:923-934.
139. Yatham LN, Paulsson B, Mullen J, Vagero AM: **Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania.** *J Clin Psychopharmacol* 2004, **24(6)**:599-606.
140. Potkin SG, Keck PE Jr., Segal S, Ice K, English P: **Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial.** *J Clin Psychopharmacol* 2005, **25(4)**:301-310.
141. Keck PE Jr., Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G: **A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania.** *Am J Psychiatry* 2003, **160(9)**:1651-1658.
142. Keck PE Jr., Versiani M, Potkin S, West SA, Giller E, Ice K: **Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial.** *Am J Psychiatry* 2003, **160(4)**:741-748.
143. Yocca F, McQuade RD, Sanchez R: **Efficacy of aripiprazole in acute mania. A new acute, placebo-controlled study: San Juan, Puerto Rico.** ; 2003.
144. Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Impellizzeri C, Kaplita S, Rollin L, Iwamoto T: **Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study.** *J Psychopharmacol* 2006, **20(4)**:536-546.
145. Schaffer A, Zuker P, Levitt A: **Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression.** *J Affect Disord* 2006, **96(1-2)**:95-99.
146. Amsterdam JD, Garcia-Espana F: **Venlafaxine monotherapy in women with bipolar II and unipolar major depression.** *J Affect Disord* 2000, **59(3)**:225-229.
147. Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Schweizer E, Beasley C: **Efficacy and safety of fluoxetine in treating bipolar II major depressive episode.** *J Clin Psychopharmacol* 1998, **18(6)**:435-440.
148. Moller HJ, Bottlender R, Grunze H, Streuss A, Wittmann J: **Are antidepressants less effective in the acute treatment of bipolar I compared to unipolar depression?** *J Affect Disord* 2001, **67**:141-146.
149. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr., Kupka RW, Denicoff KD, Nolen WA, Grunze H, Martinez MI, Post RM: **Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers.** *Am J Psychiatry* 2006, **163(2)**:232-239.
150. Post RM, Altshuler LL, Frye MA, Suppes T, Rush AJ, Keck PE Jr., McElroy SL, Denicoff KD, Leverich GS, Kupka R, Nolen WA: **Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers.** *Bipolar Disord* 2001, **3(5)**:259-265.
151. Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ: **Incidence and significance of mixed affective states in a bipolar population.** *Arch Gen Psychiatry* 1976, **33**:1062-1066.
152. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I: **Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression.** *Am J Psychiatry* 2000, **157(1)**:124-126.
153. Prien RF: **NIMH report. Five-center study clarifies use of lithium, imipramine for recurrent affective disorders.** *Hosp Community Psychiatry* 1984, **35(11)**:1097-1098.
154. Amsterdam JD, Shults J, Brunswick DJ, Hundert M: **Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate.** *Bipolar Disord* 2004, **6(1)**:75-81.
155. Ramasubbu R: **Dose-response relationship of selective serotonin reuptake inhibitors treatment-emergent hypomania in depressive disorders.** *Acta Psychiatr Scand* 2001, **104(3)**:236-8; discussion 238-9.
156. Amsterdam JD, Shults J: **Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression--lack of manic induction.** *J Affect Disord* 2005, **87(1)**:121-130.
157. Keck PE Jr., Corya SA, Altshuler LL, Ketter TA, McElroy SL, Case M, Briggs SD, Tohen M: **Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression.** *J Clin Psychiatry* 2005, **66(5)**:611-616.
158. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME: **Effectiveness of adjunctive antidepressant treatment for bipolar depression.** *N Engl J Med* 2007, **356(17)**:1711-1722.
159. Vieta E, Martinez-Aran A, Goikolea JM, Torrent C, Colom F, Benabarre A, Reinares M: **A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers.** *J Clin Psychiatry* 2002, **63(6)**:508-512.
160. Rouillon F, Serrurier D, Miller HD, Gerard MJ: **Prophylactic efficacy of maprotiline on unipolar depression relapse.** *J Clin Psychiatry* 1991, **52**:423-431.
161. Wittington C, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E: **Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data.** *The Lancet* 2004, **363**:1341-1345.
162. Privitera MR, Maharaj K: **Mania from dose-related ziprasidone augmentation of an SSRI.** *J Clin Psychiatry* 2003, **64(11)**:1393-1394.
163. FDA: <http://www.fda.gov/cder/drug/antidepressants/default.htm>. (accessed 16 October 2006).
164. Bauer MS, Wisniewski SR, Marangell LB, Chessick CA, Allen MH, Dennehy EB, Miklowitz DJ, Thase ME, Sachs GS: **Are antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).** *J Clin Psychiatry* 2006, **67(1)**:48-55.
165. Scott J, Colom F, Vieta E: **A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders.** *Int J Neuropsychopharmacol* 2006, **10(1)**:123-129.
166. Daly J, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Roose SP, Sackeim HA: **ECT in bipolar and unipolar depression: differences in speed of response.** *Bipolar Disord* 2001, **3(2)**:95-104.
167. Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, Small IF: **Electroconvulsive treatment compared with lithium in the management of manic states.** *Arch Gen Psychiatry* 1988, **45(8)**:727-732.
168. Sikdar S, Kulhara P, Avasthi A, Singh H: **Combined chlorpromazine and electroconvulsive therapy in mania.** *Br J Psychiatry* 1994, **164(6)**:806-810.
169. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L: **Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study.** *Bipolar Disord* 2002, **4 Suppl 1**:94-95.
170. Nahas Z, Kozel FA, Li X, Anderson B, George MS: **Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy.** *Bipolar Disord* 2003, **5(1)**:40-47.
171. Saba G, Rocamora JF, Kalalou K, Benadhira R, Plaze M, Lipski H, Januel D: **Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients.** *Psychiatry Res* 2004, **128(2)**:199-202.
172. Levine J, Chengappa KN, Brar JS, Gershon S, Yablonsky E, Stapf D, Kupfer DJ: **Psychotropic drug prescription patterns among patients with bipolar I disorder.** *Bipolar Disord* 2000, **2(2)**:120-130.
173. Lim PZ, Tunis SL, Edell WS, Jensik SE, Tohen M: **Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines.** *Bipolar Disord* 2001, **3(4)**:165-173.

174. Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J: **Clinical and therapeutic implications of predominant polarity in bipolar disorder.** *J Affect Disord* 2006, **93(1-3)**:13-17.

Publish with **BioMed Central** and every scientist can read your work free of charge

*"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."*

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:  
[http://www.biomedcentral.com/info/publishing\\_adv.asp](http://www.biomedcentral.com/info/publishing_adv.asp)

