Bipolar depression: clinically missed, pharmacologically mismanaged

Lisa C. Lloyd, Giovanni Giaroli, David Taylor and Derek K. Tracy

Ther Adv Psychopharmacol
(2011) 1(5) 153–162

DOI: 10.1177/
2045125311420752

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Bipolar affective disorders are common and frequently debilitating mental illnesses. Diagnostic criteria mean they are defined by the presence of pathological mood elevation, but research shows greater disease burden is inflicted by depressive phases (bipolar depression) both in terms of duration and impact of symptoms. Despite this there is consistent evidence for the underdiagnosis of bipolar depression and its misdiagnosis as a unipolar disorder, with significant subsequent impact on medication management. There is currently less robust evidence for the appropriate pharmacological approach in such individuals than in unipolar depression, and fewer guidelines for clinicians. Despite this there is clear and growing evidence that ‘treatment as usual’ of depressive symptomatology is ineffective at best, harmful at worst, and that there is little role for the use of antidepressants. Both mood stabilizers and antipsychotics demonstrate efficacy, and whilst there are emerging data on intraclass differences, more research is needed, particularly concerning bipolar II disorder. Present treatment strategies are limited by insufficient large randomized control trials, an inadequate understanding of the neuropathology of bipolar illnesses and a lack of tailored medications. Better clinical training, understanding and recognition of this common condition are essential.

Keywords: bipolar affective disorder, bipolar depression, bipolar II

Introduction

Bipolar affective disorders (BPADs) are complex mental illnesses that are frequently severe and chronic, and constitute a significant cause of disability and premature death [Nierenberg, 2008; Belmaker, 2007; Sachs *et al.* 2007; Bauer and Pfennig, 2005; Calabrese *et al.* 2005; Frye, 2011; Judd *et al.* 2003, 2002]. The lifetime risk of at least one suicide attempt ranges from 25% to 50% [Bowden, 2005; Calabrese *et al.* 2005; Dalton *et al.* 2003; Tondo *et al.* 2003; Inskip *et al.* 1998], which is clearly higher than the typically cited 15% lifetime rate reported for people with major unipolar depressive disorder (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV]). Figures on the incidence of BPADs vary depending on the criteria used and the inclusion of bipolar II disorder and subthreshold populations, but typically range from 1% to 4% [Suppes *et al.* 2010; Merikangas *et al.* 2007; Vacheron-Trystram *et al.* 2004; Akiskal *et al.* 2003; Judd *et al.* 2003, 2002; Angst, 1998].

Bipolar disorders, as the name suggests, manifest with two different spectra (or ‘poles’) of symptoms: depressive and manic (or hypomanic). The depressive phases (bipolar depression) resemble the classical description of a unipolar depressive disorder, with core symptoms of low mood, anhedonia and low energy levels as well as any of the other typical somatic and biological symptoms, such as altered sleep, appetite and libido, early morning waking, depressive ruminations, feelings of guilt, and suicidality [DSM-IV, 2000; WHO, 2004]. Bipolar disorders are further classified into at least two categories: bipolar I and bipolar II; the nature and significance of other subdiagnoses is debated, but consensus about a bipolar spectrum is emerging. Bipolar I is the classic description of an alternating mood disorder with intermittent protracted episodes of depression and pathological mood elevation. Bipolar II is similarly characterized by pathological mood variation, but depressive episodes grossly dominate the clinical picture and periods of mood elevation are typically very brief (lasting hours to days), self-limiting and nonpsychotic.

Correspondence to:
Derek K. Tracy
Consultant Psychiatrist,
Green Parks House,
Princess Royal University
Hospital, Orpington, Kent,
BR6 8 NY, UK;
Oxleas NHS Foundation
Trust;
CSI Lab, Psychological
Medicine, The Institute of
Psychiatry, King’s College
London, DeCrespigny
Park, London, UK
[derek.tracy@
oxleas.nhs.uk](mailto:derek.tracy@oxleas.nhs.uk)

Lisa C. Lloyd
CSI Lab, Psychological
Medicine, The Institute of
Psychiatry, King’s College
London, DeCrespigny
Park, London, UK

Giovanni Giaroli
North East London
Foundation Trust,
London, UK

David Taylor
Pharmacy Department,
South London and
Maudsley NHS Foundation
Trust, Denmark Hill,
London, UK;
Pharmaceutical Sciences
Division, King’s College
London, London, UK

Indeed, such symptoms can be so mild that they are frequently missed by patients and relatives as well as clinicians, often being regarded as just a relative, and positive, change in mood in relation to debilitating depression [Smith *et al.* 2010; Bauer and Pfennig, 2005]. The Zurich criteria [Angst *et al.* 2003], which are based on a 20-year prospective community cohort study, highlight that the nature of the symptoms is of more relevance than their duration, and importance should be attributed to even very brief 'highs' once the core criteria of pathological mood elevation are met.

Although bipolar disorder is defined by the occurrence of mania and hypomania and is frequently conceptualized in terms of episodic mood elevation by clinicians, depressive episodes and symptoms tend to dominate the course of the illness: they occur more frequently, last longer and lead to a greater proportion of the psychosocial disability [Bond *et al.* 2010; Frye, 2011; Sidor and Macqueen, 2010; Van Lieshout and Macqueen, 2010; Geddes *et al.* 2009; Ghaemi *et al.* 2008; Bowden, 2005; Gijsman *et al.* 2004; Judd *et al.* 2002]. Work by Judd and colleagues suggests that, in bipolar I, patients are well or asymptomatic for 53% of the time, and that during the time they are unwell manic or hypomanic states only account for 20% of the time (mixed states 13%, depressive states 67%) [Judd *et al.* 2003, 2002]. This is even starker in bipolar II, in which during the 54% of the time patients are unwell hypomanic states only account for 2% of the illness and depression accounts for 94% (mixed states taking up the remaining 4%). Kessler and colleagues highlighted the fact that work days lost per ill worker per year among patients with BPAD was greater than among those with unipolar major depression; the difference was driven primarily by recurrent depression, not mania [Kessler *et al.* 2006]. Furthermore, it typically takes longer to achieve remission in depressive than in manic phases of illness, although mixed/cycling individuals take longer again [Berk *et al.* 2005].

With such figures it is apparent that, in bipolar disorders depression is the major problem, but its accurate diagnosis and appropriate management, even when identified, has been suggested to be one of the most challenging fields in contemporary psychiatry, with a dearth of established guidelines and licensed treatments

[Fountoulakis, 2010; Frye, 2011; Smith *et al.* 2011; Suppes *et al.* 2010].

The clinical problems

Bipolar depression is clinically missed

Recognizing bipolar depression is a major challenge to most clinicians [Fountoulakis, 2010; Smith *et al.* 2011; Suppes *et al.* 2010; Sachs, 1996]. In addition to the reasons common to all mental illness (symptom overlap with other psychiatric disorders; comorbidity and substance misuse; potential lack of insight, nonengagement, nondisclosure and stigma), bipolar depression has the unique diagnostic difficulty of typically being clinically very similar to unipolar depression on mental state assessment. Patient presentation and emphasis might be most concerned with the current depressive symptomatology and focused on its alleviation, potentially forgetting, ignoring or downplaying previous manic or hypomanic symptoms; this may be even more likely in bipolar II disorder. Retrospective analysis showed that between 25% and 50% [Angst, 2007; Hirschfeld *et al.* 2003; Ghaemi *et al.* 1999] of those with bipolar depression were initially diagnosed with a unipolar illness, and the first presentation of BPAD was more likely to be with a depressive illness [Forty *et al.* 2008]. Ghaemi and colleagues showed a mean interval of 7.5 years to correct diagnosis [Ghaemi *et al.* 1999], whilst analysis of the National Depression and Manic Depression Survey in 1994 and 2000 showed that patients were typically symptomatic for more than 10 years before the correct diagnosis was made [Hirschfeld *et al.* 2003; Lish *et al.* 1994]. Delays in recognizing and diagnosing bipolar depression can prevent appropriate treatment, with serious potential implications [Berk *et al.* 2006; Bowden, 2005] including impaired social development, harmful effects from inappropriate treatment [Ghaemi *et al.* 2004] and possibly a higher risk of suicide [Baldessarini *et al.* 2006].

Although bipolar depression is very similar to unipolar depression, factors in the history and presentation might indicate the possibility of bipolar depression. Demographically, those with bipolar depression are more likely to have an earlier age of onset, a greater number of illness episodes, a positive family history of a bipolar illness and a more treatment-refractory and severe illness history [Smith *et al.* 2011; Forty *et al.* 2008; Bowden, 2005; Sharma *et al.* 2005; Geller *et al.* 2001]. The clinical presentation may show a more

atypical symptom spectrum than that of unipolar depression; although not diagnostic, there is consistent evidence for a greater incidence of hypersomnia, motor retardation, mood lability, weight gain and psychotic symptoms in bipolar depression [Forty *et al.* 2008; Bowden, 2005; Swann *et al.* 2005; Mitchell *et al.* 2001]. A particular concern, given the issue of misdiagnosis, is that more than 80% of patients with 'depression' are managed in primary care [Smith *et al.* 2011; NICE, 2006] but general practitioners will inevitably have less postgraduate training in mental health and there has been less research on bipolar depression in this environment. A recent two-phase screening study in primary care by Smith and colleagues estimated the prevalence of undiagnosed BPAD at between 3.3% and 21.6% depending on how conservatively nonresponders and those who dropped out were treated with respect to those who completed the survey: interpreting their own results, they estimate that at least 1 in 30 patients with depression in primary care have bipolar depression [Smith *et al.* 2010]. The authors suggest that screening tools might be of utility, although the particular questionnaires, the Hypomania Checklist (HCL-32) and Bipolar Spectrum Diagnostic Scale (BSDS), had high false-positive rates and low predictive values.

Bipolar depression is pharmacologically mismanaged

The treatment of unipolar depression is substantially different from that of bipolar depression, and patients with bipolar depression who are assumed to have unipolar depression will therefore receive inappropriate therapy that not only might fail to work, but can actually also worsen their condition [Sidor and MacQueen, 2010; Bowden, 2001, 2005; Ghaemi *et al.* 2000; Altshuler *et al.* 1995]. Unfortunately for clinicians, however, treatment guidelines for bipolar depression are less well defined than those for mania [Calabrese *et al.* 2005; Judd *et al.* 2002]. There is a lack of licensed treatments for bipolar depression. In the USA there are currently only three agents approved by the Food and Drug Administration: quetiapine monotherapy, olanzapine–fluoxetine combination for the acute phase of bipolar depression, and lamotrigine for maintenance and preventive treatment [Nierenberg, 2008]. Most prescribing is therefore off licence [Frye, 2011].

Antidepressant monotherapy

There is little evidence to support the efficacy of antidepressants as monotherapy in bipolar

depression, but despite this they remain the most commonly prescribed drug in all age groups [Baldessarini *et al.* 2008, 2007], being prescribed for an estimated 50% of such patients [Sidor and MacQueen, 2010; Goldberg *et al.* 2009]. An early meta-analysis by Gijsman and colleagues did show superiority over placebo in short-term treatment, but three of the four randomized controlled trials (RCTs) included were from the 1980s, two of which tested the seldom-used drugs selegiline and tranylcypromine, and the most recent one included augmentation with olanzapine in both active and placebo groups [Gijsman *et al.* 2004]. NICE's review of the evidence [NICE, 2006] found only two antidepressant RCTs rigorous enough for inclusion, of which one showed no benefit over placebo, and the other, which demonstrated superiority, again had augmentation with an antipsychotic. A meta-analysis by Sidor and MacQueen failed to show statistically significant benefit in either the acute remission or longer term recovery of patients on antidepressants compared with placebo, although there was heterogeneity in the scales and criteria used in the different studies [Sidor and MacQueen, 2010].

Monotherapeutic antidepressant use carries the risk of manic switching [Sidor and MacQueen, 2010; Truman *et al.* 2007; Henry *et al.* 2001], although it is also argued [Gijsman *et al.* 2004] that the absolute risk in early treatment is low. A recent meta-analysis [Ghaemi *et al.* 2008] suggests that antidepressant use carries a relative risk of new mania of 1.58 [95% confidence interval (CI) 0.73–3.42] compared with placebo and 2.37 (95% CI 1.38–4.05) compared with mood stabilizers, although this is debated by Sidor and MacQueen, whose meta-analysis suggests no increase in switching for selective serotonin reuptake inhibitors (SSRIs) or bupropion [Sidor and MacQueen, 2010]. However, they nuance this by arguing that cut-off criteria for switching vary: some authors have used the Young Mania Rating Scale (YMRS) to quantify affective change, but the score required to qualify as switching differs between studies, and indeed some research reports do not clearly delineate how such change was defined. Agreement on what constitutes switching remains a challenge, as does the nosological validity and long-term significance of so-called subthreshold categories. This is undoubtedly problematic for research and clinical practice, although, given the demonstrated issue of pathological mood elevation

being missed, particularly in milder instances, it would seem reasonable to conclude that many patients fall into this category with detrimental longer-term outcomes. There is evidence for interclass differences in switching, with tricyclic antidepressants showing an absolute risk difference of 6.8% (95% CI 1.7–11.9%) compared with other classes [Gijsman *et al.* 2004]. Bupropion has a lower rate of switching than dual-acting venlafaxine and tricyclic antidepressants but shows no difference compared with SSRIs [Sidor and MacQueen, 2010].

Thus, there is little valid research to support antidepressant use, and there is evidence that such medications increase the risk of affective switching.

Antidepressant augmentation therapy

Nemeroff and colleagues failed to show any statistically significant difference in the addition of either imipramine or paroxetine compared with placebo in subjects on lithium; indeed, subanalysis showed that in the high-lithium subgroup (serum levels >0.8 mmol/l) lithium and placebo was superior to lithium and an antidepressant [Nemeroff *et al.* 2001]. Ghaemi and colleagues undertook a meta-analysis of RCTs in which patients were followed up for more than 6 months: they found that addition of antidepressants to mood stabilizers was not superior to mood stabilizer monotherapy in longer-term management [Ghaemi *et al.* 2008]. Furthermore, whilst long-term treatment regimens that included antidepressants lowered the risk of recurrence of depression by 27% (pooled relative risk 0.73, 95% CI 0.55–0.97) relative to mood stabilizer monotherapy, but at the cost of a 72% increase in the risk of new episodes of mania (relative risk 1.72, 95% CI 1.23–2.41).

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a recent, large, multisite, collaborative study in BPAD that used the more naturalistic outcome measure of remaining euthymic for 8 consecutive weeks. One arm looked at bipolar depression [Sachs *et al.* 2007] in a double-blind RCT including more than 300 patients with bipolar I or II disorder who were given either a mood stabilizer and an antidepressant or a mood stabilizer and placebo. In follow up over 6 months, the addition of an antidepressant did not lead to improved outcomes, although, interestingly, there also was no increase in switching in this group, possibly

due to the protection afforded by the mood stabilizer.

Thus, even when augmenting another treatment there is little evidence to support the use of antidepressants in bipolar depression.

Mood stabilizers

Although drugs such as lithium remain a mainstay of clinical treatment in bipolar depression and a first-line treatment recommended by national guidelines [Taylor *et al.* 2009; NICE, 2006; DSM-IV, 2000], there have been relatively few high-quality studies of the use of lithium in its acute or long-term role [Van Lieshout and MacQueen, 2010]. Lithium can have long-term beneficial effects in all phases of bipolar depression [Bauer and Mitchner, 2004; Tondo *et al.* 1998]. A meta-analysis by Muzina and Calabrese showed that lithium is effective in reducing suicide and self-harm, but 30% of lithium-treated patients experienced breakthrough depression within 2 years [Muzina and Calabrese, 2005]. Pillhatsch and colleagues conducted a double-blind RCT to compare the efficacy and safety of adjunctive treatment with paroxetine or amitriptyline in 40 patients with BPAD who relapsed into a depressive episode during lithium maintenance therapy [Pillhatsch *et al.* 2010]. Although there was no comparator placebo group, patients receiving paroxetine and amitriptyline showed response rates (>50% reduction in the 21-item Hamilton Depression Rating Scale) of 76.9% and 72.2% respectively.

Lamotrigine has been advocated for bipolar depression since the mid-1990s [Calabrese *et al.* 2008], although some follow-up monotherapy studies have shown ambivalent results compared with placebo. A meta-analysis of five such RCTs combining more than 1000 patients did confirmed statistically significant efficacy, albeit modest in effect size, with benefits proportional to illness severity: the pooled relative risk for response compared with placebo was 1.27 (95% CI 1.09–1.47) on the Hamilton Rating Scale for Depression (HRSD) and 1.22 (95% CI 1.06–1.41) on the Montgomery–Asberg Depression Rating Scale (MADRS), but significance for remission was obtained only on the MADRS and not the HRSD [Geddes *et al.* 2009].

Van der Loos and colleagues undertook a double-blind RCT of lamotrigine compared with placebo in subjects already on lithium (with serum levels

between 0.6 and 1.2 mmol/l), the LamLit study, which received financial support from GlaxoSmithKline, and showed a statistically significant advantage for the combination therapy in both the primary outcome of MADRS reduction and the secondary measure of response on both the MADRS and the Clinical Global Impression-Bipolar version; there was no significant difference in switching rates between the treatments [Van der Loos *et al.* 2010]. Interestingly, follow-up work by the same group added the antidepressant paroxetine to the treatment for nonresponders in both original groups. At 8 weeks this provided statistically significant benefit to those in the lithium plus placebo group but not to nonresponders in the lithium plus lamotrigine group. The authors attribute this unexpected finding to the possible catching up of the former group in relation to the potentially plateaued latter group.

Despite its common use in mood elevation, there is a lack of high-quality research on the efficacy of sodium valproate in bipolar depression. Initial RCTs [Davis *et al.* 2005] showed superiority over placebo, but the trial size was small. The evidence has appeared stronger for preventing depressive relapse [Bowden *et al.* 2003; Calabrese *et al.* 2003a, 2003b; Gyulai *et al.* 2003] than for acute management despite it being the most commonly prescribed anticonvulsant in this condition [Bond *et al.* 2010]. The BALANCE study, a large ($n = 330$) international multisite RCT, funded in part by Sanofi-Aventis, compared valproate and lithium combination therapy with each drug in monotherapy, and showed superiority for the combination treatment over valproate monotherapy but not lithium monotherapy in preventing relapse over a 2-year period [Geddes *et al.* 2010]. This study looked at both depressive and manic relapse in bipolar I disorder, and although the authors did not set out to compare the monotherapies directly, valproate was significantly less efficacious than lithium in preventing both depressive and manic relapse. A recent systematic review and meta-analysis of four RCTs by Bond and colleagues has, however, added to the evidence in favour of this treatment, showing a relative risk of response of twice that of placebo and that of remission two thirds greater, effect sizes similar to those of quetiapine and lamotrigine [Bond *et al.* 2010].

Thus, there is evidence for efficacy with lithium, lamotrigine and sodium valproate, although the

study sizes have typically been small. Combination therapy with lithium plus another mood stabilizer may provide additional benefits for some.

Antipsychotics

Atypical antipsychotics have been used as adjuncts in severe unipolar depression [Joint Formulary Committee, 2011; Taylor *et al.* 2009]. Their efficacy in this regard has been argued to come from presynaptic serotonergic 5HT_{2C} antagonism in the prefrontal cortices, a disinhibiting effect that leads to increased release of noradrenaline and dopamine in these regions, with subsequent mood-elevating properties [Stahl, 2008]. As these drugs are also commonly used in managing the acute phase of manic and hypomanic illness, there is understandably interest in whether this class might be of benefit in bipolar depression. Antipsychotics such as quetiapine and olanzapine are being used increasingly commonly as first-line agents for many patients with bipolar depression [Calabrese *et al.* 2005; Sachs *et al.* 2004; Suppes *et al.* 2004; Ghaemi *et al.* 2003; Post *et al.* 2003; Sajatovic *et al.* 2002].

Tohen and colleagues carried out an 8-week RCT, sponsored by Lilly, involving 833 patients with bipolar depression, randomized into either olanzapine monotherapy or an olanzapine-fluoxetine combination [Tohen *et al.* 2003]. The combination was significantly more efficacious than olanzapine monotherapy and was associated with higher response and remission rates, measured on the MADRS, and lower discontinuation rates due to adverse events. The rate of switching to mania did not differ significantly between the drug combination (6.4%) and placebo (6.7%).

Quetiapine has an active metabolite, *N*-desalkylquetiapine, that appears (like reboxetine) to inhibit noradrenergic reuptake pharmacodynamically and (like buspirone) to partially agonise 5HT_{1A} [Jensen *et al.* 2008]. The actual clinical efficacy, if any, of these additional properties is unclear, although there is some early evidence (albeit industry-sponsored) suggesting a statistically significant class superiority over other antipsychotics. Owing to its relatively favourable tolerability profile it has been used across a range of mental disorders with clinical benefit [Rowe, 2007; Calabrese *et al.* 2005; Adityanjee and Schulz, 2002; Suppes *et al.* 2010].

Work by Calabrese and colleagues as part of the BOLDER (BipOLar DEpRession) study group, sponsored by Astra Zeneca, randomized 542 outpatients with bipolar depression with an acute major depressive episode to 8 weeks of quetiapine (300 or 600 mg/day) or placebo [Calabrese *et al.* 2005]. An attraction of this study is that it included patients with bipolar I disorder ($n = 360$) and patients with bipolar II disorder ($n = 182$). The percentage of patients attaining remission was 52.9% in the treatment groups overall compared with the placebo rate of 28.4% ($p < 0.001$), with low rates of subsequent mania (3.2% and 3.9%, respectively). In addition, the rate of remission was significantly shorter for both 600 mg/day (27 days) and 300 mg/day (29 days) of quetiapine compared with placebo (65 days). The higher dose of quetiapine monotherapy (600 mg) was slightly more effective but not to a statistically significant level, and was associated with more discontinuation due to more adverse events. *Post hoc* secondary analyses showed greater efficacy in the bipolar I subgroup, although the authors felt numbers were too small to draw firm conclusions from this. Both doses of quetiapine were more effective than placebo in reducing suicidal thoughts at the final assessment. The reductions with quetiapine were approximately twice that with placebo. This very large study highlights some of the core difficulties in recruiting, randomizing and retaining participants: 838 patients were screened, leading to 542 recruited, of whom only 326 completed one of the trial arms. Even in a study of this size, there were insufficient participants with bipolar II disorder to draw firm conclusions, and, as will occur in all trials to remove confounders, exclusion criteria, such as comorbid substance misuse, were such as to weaken the general applicability of the results to everyday practice.

Further bipolar depression studies of similar duration have supported quetiapine's efficacy [McElroy *et al.* 2010; Young *et al.* 2010; Thase *et al.* 2006; Calabrese *et al.* 2005]. Suppes and colleagues recently undertook an 8-week RCT of acute depression in 418 patients with bipolar depression, and showed a statistically significant advantage to the extended release (XL) formulation (single dose, 300 mg/day) compared with placebo at weeks 1 and 8 ($p < 0.001$) [Suppes *et al.* 2010]. This longer acting formulation has the natural attraction of single daily dosing with the likelihood of improved medication

concordance, although there are cost implications associated with this newer drug.

Aripiprazole, with the unique pharmacodynamic profile of a partial dopamine, 5HT_{1A} and 5HT_{2A} antagonist, has established roles in acute and maintenance treatment of manic states [Fagioli *et al.* 2011] and augmenting the treatment of unipolar depression [Marcus *et al.* 2008]. However, it has shown a lack of efficacy in both acute management and maintenance treatment of bipolar depression [Fountoulakis *et al.* 2010]. A clinical review by Yatham [2011] highlighted some improvement over placebo in the initial reduction of depressive symptoms, but not to statistically significant levels by the trial endpoints, and there was no reduction in depressive relapse rates.

Thus, there is good evidence for the use of olanzapine and quetiapine but no clear role for aripiprazole. There is growing evidence for quetiapine XL, although this might also reflect bias because the trials were sponsored by industry.

Conclusion

BPADs are common and debilitating, bipolar depression constituting the bulk of the psychosocial burden for patients. Bipolar depression can be difficult to diagnose and the evidence suggests that a significant number of patients in primary and secondary care remain mislabelled as having unipolar depression. This can lead to protracted periods before the correct diagnosis is made, with subsequent potential worsening disability and, indeed, iatrogenic deterioration from inappropriate treatments. There is an interesting disconnect between this and an apparent rapid rise in the rates of diagnosis of BPADs in clinical practice [Moreno *et al.* 2007], and there is popular media concern about overdiagnosis and the alleged influence of celebrity culture on self-diagnosis [Chan and Sireling, 2010].

A core pharmacological problem is our inadequate understanding of the neurobiology of bipolar illnesses. There is no clear corresponding neurotransmitter system or agreed pathway of dysfunction to model and therapeutically target, as occurs in unipolar depression and schizophrenia, although such theories are themselves heavily criticised and are fundamentally simplifications of more complex biological processes. Treatment has arisen largely serendipitously and haphazardly through the appropriation of medications used to treat epilepsy, unipolar depression

and, more recently, schizophrenia. As is so often the case in psychopharmacology, backward engineering of the mechanism of action has been used to try to understand both the drugs' efficacies and any underlying dysfunction. In such a scenario, our current pharmacological reality, it is perhaps understandable that our initial attempts to treat bipolar depression were based on unipolar models and that the current therapeutic arsenal is often inadequate. Nevertheless, the pharmacological reverse engineering of existing medications and molecular biology are opening up better understanding of intracellular secondary messenger systems and putative dysfunctional enzymatic components, such as inositol monophosphatase (IMPase) and glycogen synthase kinase 3 (GSK-3), that might prove more efficacious future targets for treatment [O'Brien and Klein, 2009]. The time and cost of the development of such agents will be enormous, but until this happens there is no reason why clinical practice should not follow the best current evidence.

Although there is some conflict in the literature about appropriate pharmacological treatment and a lack of clear and consistent guidelines, several clear themes emerge. Although antidepressants are by far the most commonly prescribed drug class for such patients, there is no good evidence for their use in monotherapy and very little to support their use to augment other treatments beyond the olanzapine–fluoxetine combination. In both acute and longer-term work, there is growing evidence for both mood stabilizers and antipsychotics, and within these classes lamotrigine and quetiapine respectively are showing statistically superior efficacy.

Further work is needed: better clinical guidance and psychoeducation of both patients and clinicians of this serious but treatable condition are required. Furthermore, there is a need for more RCTs in this area, particularly covering the areas of bipolar II disorder and longer-term treatment, which have to date received less attention. Finally, whilst most trials have compared an active drug with placebo, direct comparative trials between postulated treatments are needed.

Funding

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares no conflict of interest in preparing this article.

References

- Adityanjee, S.C. and Schulz, S.C. (2002) Clinical use of quetiapine in disease states other than schizophrenia. *J Clin Psychiatry* 63(Suppl 13): 32–38.
- Akiskal, H.S., Hantouche, E., Allilaire, J., Sechter, D., Bourgeois, M.L., Azorin, J. *et al.* (2003) Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). *Journal of Affective Disorders* 73(1): 65–74.
- Altshuler, L.L., Post, R.M., Leverich, G.S., Mikalaukas, K., Rosof, A. and Ackerman, L. (1995) Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry* 152: 1130–1138.
- American Psychiatric Association. (2000) Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC.
- Angst, J. (1998) The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 50: 143–151.
- Angst, J. (2007) The bipolar spectrum. *Br J Psychiatry* 190: 189–191.
- Angst, J., Gamma, A., Benazzi, F., Ajdacic, V., Eich, D. and Rossler, W. (2003) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord* 73: 133–146.
- Baldessarini, R.J., Henk, H.J., Sklar, A.R., Chang, J. and Leahy, L.F. (2008) Use of psychotropic medicines in bipolar disorder patients in the United States: combinations and adherence. *American Psychiatric Association* 59: 1175–1183.
- Baldessarini, R.J., Leahy, L.F., Arcona, S., Gause, D., Zhang, W. and Hennen, J. (2007) Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. *American Psychiatric Association* 58: 85–91.
- Baldessarini, R.J., Tondo, L., Davis, P., Pompili, M., Goodwin, F.G. and Hennen, J. (2006) Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord* 8: 625–639.
- Bauer, M. and Pfennig, A. (2005) Epidemiology of bipolar disorders. *Epilepsia* 46(Suppl 4): 8–13.
- Bauer, M.S. and Mitchner, L. (2004) What is a "mood stabilizer"? An evidence-based response. *Am J Psychiatry* 161: 3–18.
- Belmaker, R.H. (2007) Treatment of bipolar depression. *N Engl J Med* 356: 1771–1773.

- Berk, M., Berk, L., Moss, K., Dodd, S. and Malhi, S. (2006) Diagnosing bipolar disorder: how can we do it better? *Medical Journal Advances* 9(1): 1–4.
- Berk, M., Dodd, S. and Malhi, G.S. (2005) 'Bipolar missed states': the diagnosis and clinical salience of bipolar mixed states. *Aust N Z J Psychiatry* 39: 215–221.
- Bond, D.J., Lam, R.W. and Yatham, L.N. (2010) Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord* 124: 228–234.
- Bowden, C.L. (2001) Strategies to reduce misdiagnosis of bipolar depression. *Psychiatr Serv* 52: 51–55.
- Bowden, C.L. (2005) A different depression: clinical distinctions between bipolar and unipolar depression. *J Affect Disord* 84: 117–125.
- Bowden, C.L., Calabrese, J.R., Sachs, G., Yatham, L.N., Asghar, S.A., Hompland, M. *et al.* (2003) 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* 60: 392–401.
- Calabrese, J.R., Bowden, C.L., Sachs, G., Yatham, L.N., Behnke, K., Mehtonen. *et al.* (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *The Journal of Clinical Psychiatry* 64: 1013–1024.
- Calabrese, J.R., Huffman, R.F., White, R.L., Edwards, S., Thompson, T.R. and Ascher, J.A. (2008) Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *An International Journal of Psychiatry and Neurosciences* 10: 323–333.
- Calabrese, J.R., Keck, P.E., Macfadden, W., Minkwitz, M., Ketter, T.A., Weisler. *et al.* (2005) A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162: 1351–1360.
- Calabrese, J.R., Vieta, E. and Shelton, M.D. (2003b) Latest maintenance data on lamotrigine in bipolar disorder. *Eur Neuropsychopharmacol* 13(Suppl 2): S57–S66.
- Chan, D. and Sireling, L. (2010) 'I want to be bipolar' ... a new phenomenon. *The Psychiatrist* 34: 103–105.
- Dalton, J.E., Mundo, E., Parikh, S. and Kennedy, J. (2003) Suicide risk in bipolar patients: the role of co-morbid substance misuse disorder. *Am J Psychiatry* 5(1): 58–61.
- Davis, L.L., Bartolucci, A. and Petty, F. (2005) Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord* 85: 259–266.
- Fagiolini, A., Nitti, M., Forgione, R.N., Marra, F.S. and Casamassima, F. (2011) Aripiprazole for the treatment of bipolar disorder: a review of current evidence. *Expert Opin Pharmacother* 12(3): 473–488.
- Forty, L., Smith, D., Jones, L., Jones, I., Caesar, S., Cooper. *et al.* (2008) Clinical differences between bipolar and unipolar depression. *Br J Psychiatry* 192: 388–389.
- Fountoulakis, K.N. (2010) Pharmaceutical treatment of acute bipolar depression. *F1000 Med Rep* 2. <http://f1000.com/reports/m/2/47>
- Fountoulakis, K.N., Vieta, E. and Schmidt, F. (2010) Aripiprazole monotherapy in the treatment of bipolar disorder: a meta-analysis. *J Affect Disord*, DOI: 10.1016/j.jad.2010.10.018.
- Frye, M.A. (2011) Clinical practice. Bipolar disorder – a focus on depression. *N Engl J Med* 364: 51–59.
- Geddes, J.R., Calabrese, J.R. and Goodwin, G.M. (2009) Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 194: 4–9.
- Geddes, J.R., Goodwin, G.M., Rendell, J., Azorin, J.M., Cipriani, A., Ostacher, M.J. *et al.* (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 375(9712): 385–395.
- Geller, B., Zimmerman, B., Williams, M., Bolhofner, K. and Craney, J. L. (2001) Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *Am J Psychiatry* 158: 125–127.
- Ghaemi, S.N., Boiman, E.E. and Goodwin, F.K. (2000) Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry* 61: 804–808; quiz 809.
- Ghaemi, S.N., Hsu, D.J., Soldani, F. and Goodwin, F.K. (2003) Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord* 5: 421–433.
- Ghaemi, S.N., Rosenquist, K.J., Ko, J.Y., Baldassano, C.F., Kontos, N.J. and Baldessarini, R.J. (2004) Antidepressant treatment in bipolar versus unipolar depression. *Am J Psychiatry* 161: 163–165.
- Ghaemi, S.N., Sachs, G.S., Chiou, A.M., Pandurangi, A.K. and Goodwin, F.K. (1999) Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 52: 35–144.
- Ghaemi, S.N., Wingo, S.P., Filkowski, M.A. and Baldessarini, R.J. (2008) Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr Scand* 118: 347–356.
- Gijsman, H.J., Geddes, J.R., Rendell, J.M., Nolen, W.A. and Goodwin, G.M. (2004) Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 161: 1537–1547.
- Goldberg, J.F., Brooks, 3rd, J.O., Kurita, K., Hoblyn, J.C., Nassir, G., Perlis, R.H. *et al.* (2009) Depressive

- illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry* 70(2): 155–162.
- Gyulai, L., Bowden, C.L., McElroy, S.L., Calabrese, J.R., Petty, F., Swann, A.C. *et al.* (2003) Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* 28: 1374–1382.
- Henry, C., Sorbara, F., Lacoste, J., Gindre, C. and Leboyer, M. (2001) Antidepressant-induced mania in bipolar patients: identification of risk factors. *J Clin Psychiatry* 56: 1–8.
- Hirschfeld, R.M., Lewis, L. and Vornik, L.A. (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 64: 161–174.
- Inskip, H.M., Harris, E.C. and Barraclough, B. (1998) Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. *Br J Psychiatry* 172: 35–37.
- Jensen, N.H., Rodriguiz, R.M., Caron, M.G., Wetsel, W.C., Rothman, R.B. and Roth, B.L. (2008) N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT_{1A} agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* 33: 2303–2312.
- Joint Formulary Committee. (2011) *British National Formulary*, London: Pharmaceutical Press.
- Judd, L.L., Akiskal, H.S., Schettler, P.J., Coryell, W., Endicott, J., Maser, J.D. *et al.* (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 60: 261–269.
- Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A. *et al.* (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537.
- Kessler, R.C., Akiskal, H.S., Ames, M., Birnbaum, H., Greenberg, P., Robert, M.A. *et al.* (2006) Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. *Am J Psychiatry* 163: 1561–1568.
- Lish, J.D., Dime-Meenan, S., Whybrow, P.C., Price, R.A. and Hirschfeld, R.M. (1994) The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord* 31: 281–294.
- Marcus, R.N., McQuade, R.D., Carson, W.H., Hennicken, D., Fava, M., Simon, J.S. *et al.* (2008) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 28: 156–165.
- McElroy, S.L., Weisler, R.H., Chang, W., Young, A.H., Carlsson, A. and Olausson, B. (2010) A double-blind, placebo-controlled study with acute and continuation phase of Quetiapine and Paroxetine in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 71: 163–174.
- Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M.A., Petukhova, M. *et al.* (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 64: 543–552.
- Mitchell, P.B., Wilhelm, K., Parker, G., Austin, M.P., Rutgers, P. and Malhi, G. S. (2001) The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J Clin Psychiatry* 62: 212–216.
- Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A.B. and Olfson, M. (2007) National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry* 64: 1032–1039.
- Muzina, D.J. and Calabrese, J.R. (2005) Maintenance therapies in bipolar disorder: focus on randomized controlled trials. *Aust N Z J Psychiatry* 39: 652–661.
- Nemeroff, C.B., Evans, D.L., Gyulai, L., Sachs, G.S., Bowden, C.L., Gergel, I.P. *et al.* (2001) Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 158: 906–912.
- Nierenberg, A.A. (2008) An analysis of the efficacy of treatments for bipolar depression. *J Clin Psychiatry* 69(Suppl 5): 4–8.
- O'Brien, W.T. and Klein, P.S. (2009) Validating GSK3 as an in vivo target of lithium action. *Biochem Soc Trans* 37: 1133–1138.
- Pilhatsch, M., Wolf, R., Winter, C., Lewitzka, U. and Bauer, M. (2010) Comparison of paroxetine and amitriptyline as adjunct to lithium maintenance therapy in bipolar depression: a reanalysis of a randomized, double-blind study. *J Affect Disord* 126: 453–457.
- Post, R.M., Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T.M., Keck, P.E. *et al.* (2003) An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). *Bipolar Disord* 5: 310–319.
- Rowe, D.L. (2007) Off-label prescription of quetiapine in psychiatric disorders. *Expert Rev Neurother* 7: 841–852.
- Sachs, G.S. (1996) Bipolar mood disorder: practical strategies for acute and maintenance phase treatment. *J Clin Psychopharmacol* 16: 32S–47S.
- Sachs, G., Chengappa, K.N., Suppes, T., Mullen, J.A., Brecher, M., Devine, N.A. *et al.* (2004) Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord* 6: 213–223.
- Sachs, G.S., Nierenberg, A.A., Calabrese, J.R., Maragell, L.B., Wisniewski, S.R., Gyulai, L. *et al.* (2007) Effectiveness of adjunctive antidepressant

- treatment for bipolar depression. *N Engl J Med* 356: 1711–1722.
- Sajatovic, M., Mullen, J.A. and Sweitzer, D.E. (2002) Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychosis. *J Clin Psychiatry* 63: 1156–1163.
- Sharma, V., Khan, M. and Smith, A. (2005) A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affect Disord* 84: 251–257.
- Shelton, R.C. and Stahl, S.M. (2004) Risperidone and paroxetine given singly and in combination for bipolar depression. *J Clin Psychiatry* 65: 1715–1719.
- Sidor, M.M. and Macqueen, G.M. (2010) Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry* 72: 156–167.
- Smith, D.J., Griffiths, K.M., Hood, K., Craddock, N. and Simpson, S.A. (2011) Unrecognised bipolar disorder in primary care patients with depression. *Br J Psychiatry* 199: 49–56.
- Stahl, S.M. (2008) Stahl's essential psychopharmacology: neuroscientific basis and practical applications (Essential Psychopharmacology Series), 3rd edn. Cambridge: Cambridge University Press.
- Suppes, T., Datto, C., Minkwitz, M., Nordenhem, A., Walker, C. and Darko, D. (2010) Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord* 121: 106–115.
- Suppes, T., McElroy, S.L., Keck, P.E., Altshuler, L., Frye, M.A., Grunze, H. *et al.* (2004) Use of quetiapine in bipolar disorder: a case series with prospective evaluation. *Int Clin Psychopharmacol* 19: 173–174.
- Swann, A.C., Geller, B., Post, R.M., Altshuler, L., Chang, K.D., Delbello, M.P. *et al.* (2005) Practical clues to early recognition of bipolar disorder: a primary care approach. *Prim Care Companion J Clin Psychiatry* 7: 15–21.
- Taylor, D., Paton, C. and Kapur, S. (2009) The Maudsley Prescribing Guidelines, 10th edn, London: Informa Healthcare.
- Thase, M.E., Macfadden, W., Weisler, R.H., Chang, W., Paulsson, B., Khan, A. *et al.* (2006) Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 26: 600–609.
- Tohen, M., Vieta, E., Calabrese, J., Ketter, T.A., Sachs, G., Bowden, C. *et al.* (2003) Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60: 1079–1088.
- Tondo, L., Baldessarini, R., Hennen, J. and Floris, G. (1998) Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *Am J Psychiatry* 155: 638–645.
- Tondo, L., Isacson, G. and Baldessarini, R. (2003) Suicidal behaviour in bipolar disorder: risk and prevention. *CNS Drugs* 17: 491–511.
- Truman, C.J., Goldberg, J.F., Ghaemi, S.N., Baldassano, C.F., Wisniewski, S.R., Dennehy, E.B. *et al.* (2007) Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J Clin Psychiatry* 68: 1472–1479.
- Vacheron-Trystram, M.N., Braitman, A., Cheref, S. and Auffray, L. (2004) [Antipsychotics in bipolar disorders]. *Encephale* 30: 417–424.
- Van der Loos, M.L., Mulder, P., Hartong, E.G., Blom, B.J., Vergouwe, A.C., Van Noorden, M.S. *et al.* (2010) Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine. *Acta Psychiatr Scand* 122: 246–254.
- Van Lieshout, R.J. and MacQueen, G.M. (2010) Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. *Br J Psychiatry* 196: 266–273.
- World Health Organisation (2004). International Statistical Classification of Diseases and Health Related Problems. Geneva: World Health Organization.
- Yatham, L.N. (2011) A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder. *J Affect Disord* 128(Suppl 1): S21–S28.
- Young, A.H., McElroy, S.L., Bauer, M., Philips, N., Chang, W., Olausson, B. *et al.* (2010) A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 71: 150–162.