Dimos Dimellis[1], Konstantinos N. Fountoulakis[2]

[1] 3rd Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Greece;
[2] Assistant professor, 3rd Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Greece

PHARMACOEPIDEMIOLOGY OF BIPOLAR DISORDER: A REVIEW

Abstract

Introduction: Pharmaco-epidemiological research by reflecting the use of drugs in real life situations, is crucial in exploring important public health issues related to psychotropic drug use, such as the medical and economic impact of unjustified extension of use, the identification of infrequent or delayed adverse effects, and the efficiency of new marketed products in naturalistic conditions. The scope of the current presentation is to review systematically the available data on the treatment of bipolar disorder.

Material and methods: A systematic MEDLINE search, concerning the treatment of bipolar disorder with 'mania', 'manic', 'bipolar', 'manic-depression', 'manic-depressive' with 'pharmacoepidemiology' or 'prescription' or 'prescription patterns' or 'therapeutic practice'as keywords, was performed.

Results: The literature suggests that the treatment of bipolar disorder is driven by symptomatology and falls short of the existing guidelines. Regarding acute mania, the use of antipsychotics is preferred over lithium or anticonvulsants either as monotherapy or as combination treatment. The data about bipolar depression are scarce and limited although the use of antidepressants is more common in everyday practice than the guidelines advice. Finally, as for the maintenance phase, the use of lithium seems to vary worldwide, whereas the use of antipsychotics is common, especially for those patients with psychotic features or with more complicated course. Astonishingly, 25-50% of bipolar patients are, cross-sectionally, under antidepressants. Overall, less than 40% of patients are on monotherapy and the percentage is falling, while polypharmacy seems to dominate the pharmacotherapy of bipolar disorder, with up to 50% of patients receiving 3 or more psychoactive drugs at the same time.

Conclusions: Available data confirm that clinicians do not follow, at least strictly, the proposed guidelines. On the other hand, the effectiveness of the available treatments lies far from ideal, a fact that offers a ground for combinations, despite their increased burden of side effects. There is abundant room for further progress in determining more "clinician friendly" guidelines and treatment choices.

Key words: Bipolar disorder, aniconvulsants, antidepressants, antipsychotics, lithium, mood stabilizers, treatment, pharmacoepidemiology

Introduction

Traditionally the understanding of bipolar disorder (BD) suggested that it is an episodic illness with a return to premorbid level of functioning between the episodes and a favourable outcome in comparison to schizophrenia [1]. Today we know that this is not always the case [2] and the Kraepelinian concept largely corresponds to BD-I. Frequently there is a delay of several years before the correct diagnosis is being put.

Delaying correct diagnosis has profound implications concerning the choice of treatment and its overall efficacy, as treatment differs according to diagnosis. Consequently, treatment outcome might be suboptimal. This outcome is, also, strongly related to younger age of onset and to alcohol and substance abuse. Another important issue is the associated with mood disorders suicidality. Finally, regarding the resulting, overall

Correspondence

Dimos Dimellis
dimosdimellis@hotmail.com

disability BD has been ranked amongst the 10 most disabling medical conditions world-wide by the World Health Organization (WHO) [3].

The treatment of bipolar illness is not only affected by the correct diagnosis but it is, also, complex and full of caveats for the clinician [4-7]. It is true that the earlier studies tended to suggest a high and global effectiveness for older agents on all facets of BD and a high prevalence of switching with antidepressants constructing the widespread concept of 'class effect'. Neither conclusion is confirmed by newer studies and the recent data suggest that it is doubtful any class effect is present, maybe except from the efficacy of antipsychotics against acute mania.

From a clinical point of view, depression and the maintenance phase seem to be more important since effective treatments are much fewer in comparison to acute mania. In this frame, while evidence based medicine seems to dominate medical scientific thinking in the last decades, this is not true for the wider clinical practice, mainly because the evidence is limited and hard to interpret and to carry in everyday practice. On the other hand, it is highly likely that a significant number of bipolar patients worldwide are not recieving proper treatment simply because continued scientific training and reading is inadequate. Focused educational intervention might be nessessary to change this attitude.

Pharmaco-epidemiological research is crucial in order to explore important public health issues related to psychotropic drug use, such as the medical and economic impact of unjustified extension of use, the identification of infrequent or delayed adverse effects, and the efficiency of new marketed products in naturalistic conditions [8]. The scope of the current review was to explore the pharmaco-epidemiological data of BD the way the average psychiatrist treats patients.

Material and Method

The MEDLINE was searched in order to locate papers with concerning the pharmacoepidemiology of BD. The search strategy inlcuded the combination of each one of the key words 'mania', 'manic', 'bipolar', 'manic-depression', 'manic-depressive' with 'pharmacoepidemiology' or 'prescription' or 'prescription patterns' or 'therapeutic practice'. The search strategy was augmented through the inspection of reference lists of relevant review articles. Eligible articles included original studies in English.

Two investigators (KNF and DD) independently reviewed articles for eligibility. If either deemed an article as potentially eligible based on title/abstract review, then a full-text review was performed. The references of retrieved articles were hand-searched for further relevant articles and other relevant data were included. Final decisions regarding the eligibility were made by consensus following the full-text review.

Acute mania

There are not much data on the real world clinical practice concerning the pharmacotherapy of acute bipolar mania. The first studies revealed a cautionary attitude towards lithium and antiepileptics during the acute manic phase and a favor of typical antipsychotics. The review of therapeutic practices from two psychiatric care centres in Germany between 1975 und 1991 revealed that neuroleptics were preferred over lithium and carbamazepine. Combinations of more potent antipsychotics with more sedative neuroleptics were usual [9]. In the 1980s a decrease in the frequency of neuroleptic monotherapy and an increased proportion of combined treatments with lithium or carbamazepine were observed, however lithium and antiepileptics were still not widely accepted 10. On the contrary, in Japan it was reported that lithium was the most popular treatment for bipolar mania [11].

More recent studies, after the introduction of atypical antipsychotics showed a resistance of these attitudes. The study of treatment patterns at the University department of Psychiatry in Vienna Austria from 1997 to 1999 revealed that international guidelines were not included in daily practice with regard to the usage pattern of atypical antipsychotics versus typical neuroleptics or concerning monotherapy with a mood stabilizer as first-line treatment for acute mania as polypharmacy was the predominant treatment scheme [12]. Before the establishment of second generation antipsychotics as effective antimanic agents, it has been reported that overall, 84.7% of bipolar patients received typical antipsychotic agents; 53.8% was on monotherapy and 47.4% in combination with a mood stabilizer [13]. The evaluation of treatment practices against acute mania in a private psychiatric hospital in Brazil, from 1996 to 2000 revealed that the most frequent agents used were antipsychotics (83.3%) followed by lithium (71.5%), carbamazepine (34.8%), valproate (9.4%) and ECT (33.2%). There was a frequent concomitant use of ECT with lithium (72.3%) [14]. An epidemiologic study from the US on first-admission bipolar patients with psychotic features suggested that more patients received antipsychotics (80.0%) than lithium or antiepileptics (52.3%)

at discharge. After two years, 44.6% reported using no medications while 19.4% and 38.8% were taking antipsychotics and antimanics, respectively [15].

Acute bipolar depression

Pharmacoepidemiological data are rare concerning the treatment of bipolar depression. An unpublished poster presentation from Japan reported that the Japanesse psychiatrists were divided between antidepressants and mood stabilizers on the treatment of bipolar depression [11]. An old study from the '90s utilized the pharmacy records of the McLean Hospital from 1987 to 1993 and reported that 3829 bipolar depressive inpatients had received tricyclic antidepressants, 2981 fluoxetine, 2603 trazodone, 809 bupropion, 743 monoamine oxidase inhibitors, 592 stimulants, 588 sertraline, 48 paroxetine, and 894 ECT [16].

Maintenance treatment

There are several pharmacoepidemiological studies exploring prescription patterns, especially concerning lithium, monotherapy *vs* combination therapy, the discrepancy between official treatment guidelines and clinical practice as well as the change in patterns with the introduction of atypical antipsychotics and SSRIs. The studies cover a broad spectrum of data bases and come from the US [17-27], Denmark, Norway and Sweden [28 29], the Netherlands [30] Spain [31], Hungary [32], and the UK [33 34].

The prevalence of lithium treatment for the years 2005-6 was estimated between 17 and 25 per 10,000 persons of the general population in Denmark, Norway and Sweden [29]. In the Netherlands, during 1996-2005, the use was significantly lower with 9.5-12 per 10,000 persons [30]. USA data from the Oregon Medicaid during 1998-2003 reported that 25% of bipolar patients were receiving lithium, which corresponds to 12.5-25 persons per 10,000 [18]. Data from the clinical database of the Palo Alto Veterans Affairs Medical Center for the years 1989-95 suggested that there was a decline in the rate of lithium monotherapy for treatment of bipolar affective disorder from 84% to 43% (43 per 10,000 persons) [26]. The STEP-BD data suggest that lithium was prescribed to 37.8% of younger patients compared with only 29.5% of older participants [19]. The 2002-2003 U.S. national MarketScan database data suggest that 8% of bipolar patients were on lithium with almost half of them being on monotherapy which was more long-standing than with other stabilizers [21]. Thus US pharmacoepidemiological data for lithium vary widely (from 8-50 per 10,000) probably depending on sampling while also race seems to play a role with blacks being significantly less likely to receive lithium [22]. Overall pharmacoepidemiological data from around the world suggest that lithium use varies from 8-50 per 10,000 persons of the general population and the reason for this remains to be clarified [31 33]. Data from Germany suggested that the majority of patients (54.3%) were under monotherapy while 39.3% of patients were receiving two agents, and 6.6% three agents. Antidepressants (64.1%) were the most common combination medications [35].

The frequency of combination therapy is another question. According to most RCTs almost half of patients do not respond to monotherapy treatment during the acute manic phase. Thus it is expected that combination treatment will be widely spread in everyday clinical practice [17 32]. The 2002-2003 U.S. national MarketScan research databases suggest that only 44% of patients were receiving monotherapy. Median time to adding another psychotropic was 2.5-times less than median time to changing the initial treatment (16.4 compared with 40.9 weeks), and stopping was rare. An increase in the number of psychotropic medications prescribed across years 1996-2006 has been recorded; visits with 2 or more medications increased from 42.6% in 1996-1997 to 59.8% in 2005-2006; visits with 3 or more medications increased from 16.9% to 33.2%. Prescription for 2 or more antidepressants, antipsychotics, sedative-hypnotics, and antidepressant-antipsychotic combinations, but not other combinations, significantly increased across survey years. There was no increase in prescription of mood stabilizer combinations [27]. Intake treatment data for the first 500 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (1998 to 1999) revealed that only 11 % of patients were treated with standard mood stabilizer monotherapy [23], while latter it has been reported that on average, participants who reached a recovered status took 2.05 medications with no difference between age groups [19].

Suicidality is reported to relate to more complex treatment patterns [17] while in comparison to lithium treated, divalproex treated patients were reported to had had 1.5 and gabapentin 2.6 hazard ratio of commiting suicide while data for carbamazepine are not available [18].

The above suggest that only 10-40% of patients are on monotherapy and the percentage is falling; on the contrary polypharmacy is increasingly becoming eve-

ryday practice with 25-50% receiving three or more agents simultaneously, with a trend towards increasing number of agents.

An old dilemma was also the US *vs* Europe approach to the treatment of BD meaning the preferable use of lithium and anticonvulsants *vs* antipsychotics and antidepressants; this dilemma was weakend with the recent approval of atypical antipsychotics for the treatment of BD. However even before that approval, the pharmacoepidemiological data suggest that a significant proportion of patients were under antipsychotics, including typical.

US data suggest that in privately insured individuals aged 18-64 during the years 1994-1998, first-generation antipsychotics were used by 16.4% of patients and second-generation agents by 12.4%. Patients starting on antipsychotics tended to stay with them for 12 months or longer, while patients starting on anticonvulsants were more likely to stop therapy or to switch to another medication class [24]. Also a subset of data from a larger voluntary registry on non-hospitalized subjects with bipolar I disorder in 1995/96 suggested that nearly one-third of all patients were receiving antipsychotic agents (66% typical) [25]. The 2002-2003 U.S. national MarketScan research databases suggest that mood stabilizers were more frequently prescribed as first drug than antipsychotics (25% *vs* 11%) with 17% anticonvulsants and 8% lithium. Overall half of patients were on lithium and one third on antipsychotics and the median weeks until therapy was changed in any way was 29 weeks for lithium *vs* 13 for antipsychotics [21]. Intake treatment data for the first 500 patients in the STEP-BD study (1998 to 1999) revealed that standard mood stabilizers (lithium, valproate, or carbamazepine) were the most commonly prescribed class of drugs that participants were taking at intake (71.9 %), followed by novel anticonvulsants (31.8%), *vs* second-generation neuroleptics (27.2%) [23]. The UK data from the case note review of the pharmacotherapy from a specified South London sector of a National Health Service Trust suggested that half of the patients were on mood-stabilizers (usually lithium) and their use was associated with female gender and multiple admissions. Antipsychotics were more commonly used in patients with psychotic features and multiple manic episodes [34]. The case note review of North-East of England suggested antipsychotic use was almost equally split between typical and atypical drugs [33]. The Prescribing Observatory for Mental Health reviewed data from 35 National Health Service Trusts on 2776 patients with a diagnosis of affective illness. These data suggested that 10% of patients had lithium levels below the therapeutic range and that co-prescribing of lithim plus antipsychotics was common (57%) [36].

US data suggest that race also influences with blacks being less likely to receive lithium and significantly more likely to receive first-generation antipsychotics and any antipsychotic and less likely lithium and SSRIs [22].

A similar picture was found concerning antidepressants. The US data from non-hospitalized subjects with bipolar I disorder in 1995/96 suggested that more than half of all subjects were receiving concomitant antidepressants, of whom nearly 50% received the SSRI antidepressants and nearly 25% received buproprion [25]. The data from the 2002-2003 U.S. national MarketScan research databases data suggest that the most commonly prescribed first drug class was antidepressants (50% of patients) [21]. Intake treatment data for the first 500 patients in the STEP-BD study (1998 to 1999) revealed that the second most common class of agents was antidepressants (40.6 %) [23].

In the Netherlands the search of prescription patterns during 1996-2005 revealed a significant decrease in the use of tricyclic antidepressants, which, however were still in wide use [30]. A small Hungarian study reported that 35% of patients was on antidepressants and more than half of them on SSRI, which implies a sustained wide use of tricyclics [32]. The UK data from the case note review of North-East of England suggested that 23% of patients were on antidepressants; 11% of them were not prescribed a mood stabilizer and 43% of antidepressants prescribed were tricyclics [33], while the case note review of South London National Health Service Trust on the contrary reported that antidepressants were rarely prescribed alone [34].

Taken the above together, it seems that depending on the sample, 25-50% of bipolar patients are cross-sectionally under antidepressants, with almost half of them receiving tricyclics, sometimes without concomitant antimanic agents.

Discussion

The earlier studies suggest a high and global effectiveness for older agents on all facets of BD and a high prevalence of switching with antidepressants, which were not confirmed by newer studies. On the other hand, these old agents are considered to be the 'gold standard' and are used as comparators in randomized trials of newer drugs. Since some of these studies are superiority ones, the literature could include data that might be misleading concerning the

older agents and in favour of newer drugs. This is a bias inherent in the literature and it should be taken into consideration when interpreting the data. Another possible source of bias is the fact that today the use of lithium is much more widespread and patients with a favorable response are unwilling to participate in a study with the risk of dropping it. This fact might have led to the inclusion of a disproportionally percentage of refractory to lithium patients and also of patients suffering from milder symptomatology in most recent studies [37]. Another problem with recent trials is the high dropout rate that limits the generalizability of the results [38 39]. Those high attrition rates, however, may be in part attributable to higher ethical standards in modern studies.

On the other hand, it is widely accepted that lithium possesses a specific anti-suicidal effect [40-48] and this is supported by a systematic review [49], although there is some concern that there was an over-interpretation of data [50]. However the STEP-BD study results do not support this [51]. Lithium is more effective against mania and to a lesser degree against depression [40 52-54]. Some patients appear to develop a tolerance to lithium after several years of successful use; a lithium discontinuation-induced refractoriness is also reported in up to 15% of patients [55]. Patients with an episodic course with euthymic intervals, and the absence of rapid cycling may respond better to lithium [56-60]. It is unclear whether after plolonged treatment it exerts a neuroprotective or a neurotoxic effect [61] and its mode of action is unclear [62]. Adverse effects are to be expected during lithium therapy [63].

Only antipsychotics possess such a 'class effect' against acute mania, while it is clear that there is no 'class effect' of any kind concerning either antiepileptics or antidepressants. This is of high importance since it seems that most clinicians consider that such an effect is the rule rather than the exception. If this proves to be so, then many patients worldwide might receive inappropriate treatment.

Regarding entipepileptics both valproate and carbamazepine are approved by the FDA for the treatment of acute manic episodes. A different case is lamotrigine, which is approved only for maintenance treatment. Several experts and drug licensing authorities do not consider its data strong enough [64] to merit an acute bipolar depression label. In spite of this, response rates against depression are reported to be 50% and are double than those observed under placebo [65]. The U.S. Food and Drug Administration (FDA) has already approved 6 SGAs for the treatment of acute mania: olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole and asenapine. These drugs are also approved for the treatment of mania in most European countries. Quetiapine and Lurasidone currently are the only SGAs with an FDA indication against bipolar depression as monotherapy. Olanzapine is approved for mania and the maintenance phase, and OFC for depression, while aripiprazole is also approved for mania and the maintenance phase. First generation (typical) antipsychotics (FGAs) and especially haloperidol, were used for long especially for the treatment of acute mania and were considered to act faster than mood stabilizers, however the anecdotal clinical impression may psychiatrists have is that they induce depression was recently supported by two studies [66]. A recent review suggests that the magnitude of improvement was similar whether the SGAs were utilized as monotherapy or adjunctive therapy [67]. If the patient has a life history of predominant manic or mixed episodes with rare and short depressive episodes, the administration of an SGA alone could be enough to control the disorder [68].

The most controversial of all classes of agents used in BD is antidepressants. Fluoxetine is the only antidepressant with official approval by the FDA for use in BD, not as monotherapy, but in combination with olanzapine. The use and usefulness of antidepressant agents in BD is controversial. Even their true effectiveness has been questioned, in spite of the randomized studies and the conclusion of a recent systematic review [69]. Guidelines suggest their cautious use and always in combination with an antimanic agent [6]. This is because antidepressants are believed to induce switching to mania or hypomania [70-73] mixed episodes [74] and rapid cycling, while research suggests that the use of antimanic agents might protect from such an effect [75]. Earlier studies pointed this problem especially with tricyclics [76-78] **44** however this may not be exactly the case with newer compounds. Some authors suggest the true rate of switching is rather low [79-81], while most studies reporting such an effect suffer from serious methodological problems while a strong publication bias is likely to be present [82]. The recent STEP-BD study produced equivocal results but generally they do not support the concept that antidepressant use worsens the course of the illness [83-86].

Beyond this reasonable doubt concerning the dangers of antidepressant use, the general concept is that dual action agents (TCAs or SNRIs) may be more potent in increasing the risk for switching to mania or hypomania [70] and to suicide [87 88]. Bipolar

II patients could be at the highest risk [89]. The concomitant use of an antimanic agent (atypical antipsychotic or anticonvulsant) may protect against switching or mixed symptoms, but this does not happen always [70 90]. However, on the contrary, in patients more prone to experience depressive episodes the continuation treatment with antidepressants might be beneficial [91-93].

Most authors agree that after the second episode of bipolar illness, long-term treatment is necessary, but this may still be too conservative, with most patients actually benefiting from early lifelong therapy. This treatment is based on the use of lithium, aripiprazole, olanzapine or olanzapine-fluoxetine combination, quetiapine and lamotrigine either as monotherapy or in combination. Traditional choices like valproate do not have sufficient scientific support. The choice depends largely on the longitudinal course of the illness and the predominant polarity of the episodes as well as previous response to a specific agent. Although it has been claimed that maintenance treatment should last at least 2 years after an episode or 5 years if the patient has risk factors for relapse [94], in clinical practice it is better to plan for lifetime treatment unless contraindications or specific issues would go against it.

Conclusively, pharmaco-epidemiological studies revealed early that clinicians do not follow treatment recommendations made by experts and it is unlikely they base their judgement on research data [8]. This was stricking in the case of first generation antipsychotics *vs* antiepileptics [95] as well as concerning the use of antidepressants [16]. Esprecially, regarding antidepressants, literature suggest that they represent the most commonly prescribed class of psychotropics in BD with 25-50% receiving one [21 25]. Furthermore, combination seems to be the preffered treatment choice over monotherapy [23 17]. The general picture from pharmaco-epidemiological studies is that in everyday ordinary care, the treatment of bipolar patients is often driven by symptoms and falls short of the existing practice guidelines [34].

Take home messages for psychiatric care

- Literature overall, and especially regarding bipolar depression, is scarce and limited
- Symptomatology rather, than guidelines, drives the choice of treatment thus clinicians do not follow strictly the proposed guidelines
- Acute mania: Antipsychotics are preferred over mood stabilizers-anticonvulsants
- Acute bipolar depression: The use of antidepressants is more common than the guidelines suggest
- Maintenance phase: Polypharmacy dominates monotherapy. The use of lithium varies while as much as 50% of bipolar patients are on antidepressants

References

1 Kraepelin E. *Manic-depressive insanity and paranoia*. Edinburgh, Livingstone 1921.

2 Tohen M, Waternaux CM, Tsuang MT. *Outcome in Mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis*. Arch Gen Psychiatry 1990;47:1106-11.

3 World Health Organization. *The world health report 2003 - shaping the future*. Geneva WHO 2003.

4 Fountoulakis KN, Grunze H, Panagiotidis P, et al. *Treatment of bipolar depression: an update*. J Affect Disord 2008;109:21-34.

5 Fountoulakis KN, Magiria S, Siamouli M, et al. *A seven- year follow-up of an extremely refractory bipolar I patient*. CNS Spectr 2007;12:733-4.

6 Fountoulakis KN, Vieta E, Sanchez-Moreno J, et al. *Treatment guidelines for bipolar disorder: a critical review*. J Affect Disord 2005;86:1-10.

7 Fountoulakis KN, Vieta E, Siamouli M, et al. *Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder*. Ann Gen Psychiatry 2007;6:27.

8 Verdoux H, Begaud B. *Pharmaco-epidemiology: what do (and don't) we know about utilisation and impact of psychotropic medications in real-life conditions?* Br J Psychiatry 2004;185:93-4.

9 Adler L, Ulrich M, Lehmann K, et al. *General practice of acute inpatient treatment of mania. Retrospective comparative study of 100 patients at each of 2 psychiatric centers*. Fortschr Neurol Psychiatr 1994;62:479-88.

10 Reetz-Kokott U, Muller-Oerlinghausen B. *Has drug treatment of manic disorders changed in clinical routine practice? Retrospective analysis of treatment modalities and results in a university psychiatric clinic*. Nervenarzt 1996;67:229-34.

11 Oshima A, Higuchi T, Fujiwara Y, et al. *Questionnaire survey on the prescribing practice of Japanese psychiatrists for mood disorders*. Psychiatry Clin Neurosci 1999;53:S67-72.

12 Letmaier M, Schreinzer D, Thierry N, et al. *Drug therapy of acute manias. A retrospective data analysis of inpatients from 1997 to 1999*. Nervenarzt 2004;75:249-57.

13 Tohen M, Zhang F, Taylor CC, et al. *A meta-analysis of the use of typical antipsychotic agents in bipolar disorder*. J Affect Disord 2001;65:85-93.

14 Volpe FM, Tavares A, Correa H. *Naturalistic evaluation of inpatient treatment of mania in a private Brazilian psychiatric hospital*. Rev Bras Psiquiatr 2003;25:72-7.

15 Craig TJ, Grossman S, Mojtabai R, et al. *Medication use patterns and 2-year outcome in first-admission bipolar disorder with psychotic features*. Bipolar Disord 2004;6:406-15.

16 Zarate CA JR, Tohen M, Baraibar G. *Prescribing trends of antidepressants in bipolar depression*. J Clin Psychiatry 1995;56:260-4.

17 Goldberg Jf, Brooks Jo, 3rd, Kurita K, et al. *Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD*. J Clin Psychiatry 2009;70:155-62.

18 Collins Jc, Mcfarland Bh. *Divalproex, lithium and suicide among Medicaid patients with bipolar disorder*. J Affect Disord 2008;107:23-8.

19 Al Jurdi Rk, Marangell Lb, Petersen Nj, et al. *Prescription patterns of psychotropic medications in elderly compared with younger participants who achieved a "recovered" status in the systematic treatment enhancement program for bipolar disorder*. Am J Geriatr Psychiatry 2008;16:922-33.

20 Zhu B, Kulkarni Pm, Stensland Md, et al. *Medication patterns and costs associated with olanzapine and other atypical antipsychotics in the treatment of bipolar disorder*. Curr Med Res Opin 2007;23:2805-14.

21 Baldessarini Rj, Leahy L, Arcona S, et al. *Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders*. Psychiatr Serv 2007;58:85-91.

22 Kilbourne Am, Pincus Ha. *Patterns of psychotropic medication use by race among veterans with bipolar disorder*. Psychiatr Serv 2006;57:123-6.

23 Ghaemi Sn, Hsu Dj, Thase Me, et al. *Pharmacological treatment patterns at study entry for the first 500 step-bd participants*. Psychiatr Serv 2006;57:660-5.

24 Russo P, Smith Mw, Dirani R, et al. *Pharmacotherapy patterns in the treatment of bipolar disorder*. Bipolar Disord 2002;4:366-77.

25 Levine J, Chengappa Kn, Brar Js, et al. *Psychotropic drug prescription patterns among patients with bipolar I disorder*. Bipolar Disord 2000;2:120-30.

26 Fenn Hh, Robinson D, Luby V, et al. *Trends in pharmacotherapy of Schizoaffective and bipolar affective disorders: a 5-year naturalistic study*. Am J Psychiatry 1996;153:711-3.

27 Mojtabai R, Olfson M. *National trends in psychotropic medication polypharmacy in office-based psychiatry*. Arch Gen Psychiatry 2010;67:26-36.

28 Vestergaard P, Schou M. *Lithium treatment in Aarhus*. 1. Prevalence. Pharmacopsychiatry 1989;22:99-100.

29 Bramness JG, Weitoft GR, Hallas J. *Use of lithium in the adult populations of Denmark, Norway and Sweden*. J Affect Disord 2009;118:224-8.

30 Wilting I, Souverein PC, Nolen WA, et al. *Changes in outpatient lithium treatment in the Netherlands during 1996-2005*. J Affect Disord 2008;111;94-9.

31 Castells X, Vallano A, Rigau D, et al. *Trends in lithium prescription in Spain from 1985 to 2003*. J Affect Disord 2006;91:273-6.

32 Kovacs G. *Pharmacotherapeutic trends at the beginning of the millennium in Hungary. Pharmacotherapy for bipolar patients, I*. Neuropsychopharmacol Hung 2004;6:13-8.

33 Lloyd AJ, Harrison CL, Ferrier I, et al. *The pharmacological treatment of bipolar affective disorder: practice is improving but could still be better*. J Psychopharmacol 2003;17:230-3.

34 Frangou S, Raymont V, Bettany D. T*he Maudsley bipolar disorder project. A survey of psychotropic prescribing patterns in bipolar I disorder*. Bipolar Disord 2002;4:378-85.

35 Quante A, Zeugmann S, Regen F, et al. *Psychopharmacological treatment status in outpatients with bipolar disorder: a clinical survey in Germany*. Psychiatry Investig 2010;7:155-62.

36 Paton C, Barnes TR, Shingleton-Smith A, et al. *Lithium in bipolar and other affective disorders: prescribing practice in the UK*. J Psychopharmacol 2010;24:1739-46.

37 Burgess S, Geddes J, Hawton K, et al. *Lithium for maintenance treatment of mood disorders*. Cochrane Database Syst Rev 2001 CD003013.

38 Rendell JM, Gijsman HJ, Keck P, et al. *Olanzapine alone or in combination for acute mania*. Cochrane Database Syst Rev 2003 CD004040.

39 Rendell JM, Gijsman HJ, Bauer MS, et al. *Risperidone alone or in combination for acute mania*. Cochrane Database Syst Rev 2006 CD004043.

40 Grunze H, Kasper S, Goodwin G, et al. *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;5:120-35.

41 Geddes JR, Burgess S, Hawton K, et al. *Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials*. Am J Psychiatry 2004;161:217-22.

42 Baldessarini RJ, Tondo L, Hennen J. *Lithium treatment and suicide risk in major affective disorders: update and new findings*. J Clin Psychiatry 2003;64:44-52.

43 Calabrese JR, Goldberg JF, Ketter TA, et al. *Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies*. Biol Psychiatry 2006;59:1061-4.

44 Prien RF, Kupfer DJ, Mansky PA, et al. *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;41:1096-104.

45 Kane JM, Quitkin FM, Rifkin A, et al. *Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison*. Arch Gen Psychiatry 1982;39:1065-9.

46 Bech P, Vendsborg PB, Rafaelsen OJ. *Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine*. Acta Psychiatr Scand 1976;53:70-81.

47 Bowden CL, Brugger AM, Swann AC, et al. *Efficacy of divalproex vs lithium and placebo in the treatment of mania*. The Depakote Mania Study Group. Jama 1994;271:918-24.

48 Kessing LV, Sondergard L, Kvist K, et al. *Suicide risk in patients treated with lithium*. Arch Gen Psychiatry 2005;62:860-6.

49 Cipriani A, Pretty H, Hawton K, et al. *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, 1805-19.

50 Connemann BJ. *Lithium and suicidality revisited*. Am J Psychiatry 2006;163:550; author reply 550-1.

51 Goldberg JF, Allen MH, Miklowitz DA, et al. *Suicidal ideation and pharmacotherapy among STEP-BD patients*. Psychiatr Serv 2005;56:1534-40.

52 Calabrese JR, Vieta E, Shelton MD. *Latest maintenance data on lamotrigine in bipolar disorder*. Eur Neuropsychopharmacol 2003;13:S57-66.

53 Goldsmith Dr, Wagstaff AJ, Ibbotson T, et al. *Spotlight on lamotrigine in bipolar disorder*. CNS Drugs 2004;18:63-7.

54 Bauer Ms, Callahan Am, Jampala C, et al. *Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs*. J Clin Psychiatry 1999;60:9-21.

55 Post R, Leverich G, Altshuler L, et al. *Lithium-discontinuation-induced refractoriness: Preliminary observations*. Am J Psychiatry 1992;149:1727.

56 Grof P. *Selecting effective long-term treatment for bipolar patients: monotherapy and combinations*. J Clin Psychiatry 2003;64:53-61.

57 Grof P, Duffy A, Cavazzoni P, et al. *Is response to prophylactic lithium a familial trait?* J Clin Psychiatry 2002;63:942-7.

[58] Grof P, Alda M, Grof E, et al. *Lithium response and genetics of affective disorders*. J Affect Disord 1994;32:85-95.

[59] Faedda GL, Baldessarini RJ, Tohen M, et al. *Episode sequence in bipolar disorder and response to lithium treatment*. Am J Psychiatry 1991;148:1237-9.

[60] Bowden CL, Calabrese JR, Mcelroy SL, et al. *A randomized placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder*. Arch Gen Psychiatry 2000;57:481-489.

[61] Fountoulakis KN, Vieta E, Bouras C, et al. *A systematic review of existing data on long-term lithium therapy: neuroprotective or neurotoxic?* Int J Neuropsychopharmacol 2008b;11:269-87.

[62] Wu RH, O'donnell T, Ulrich M, et al. *Brain choline concentrations may not be altered in euthymic bipolar disorder patients chronically treated with either lithium or sodium valproate*. Ann Gen Hosp Psychiatry 2004;3:13.

[63] Silverstone PH, Bell EC, Willson MC, et al. *Lithium alters brain activation in bipolar disorder in a task- and state-dependent manner: an fMRI study*. Ann Gen Psychiatry 2005;4:14.

[64] Brown EB, Mcelroy SL, Keck PE, et al. *A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression*. J Clin Psychiatry 2006;67:1025-33.

[65] Calabrese JR, Bowden CL, Sachs GS, et al. *A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression*. Lamictal 602 Study Group. J Clin Psychiatry 1999;60:79-88.

[66] Zarate CA Jr, Tohen M. *Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients*. Am J Psychiatry 2004;161:169-71.

[67] Perlis RH, Welge JA, Vornik LA, et al. *Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials*. J Clin Psychiatry 2006;67:509-16.

[68] Colom F, Vieta E, Daban C, et al. *Clinical and therapeutic implications of predominant polarity in bipolar disorder*. J Affect Disord 2006;93:13-7.

[69] Gijsman HJ, Geddes JR, Rendell JM, et al. *Antidepressants for bipolar depression: a systematic review of randomized, controlled trials*. Am J Psychiatry 2004;161:1537-47.

[70] Moller H, Bottlender R, Grunze H, et al. *Are antidepressant less effective in the acute treatment of bipolar I compared to unipolar depression?* J Affect Disord 2001;67:141-6.

[71] Post RM, Altshuler LL, Leverich GS, et al. *Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline*. Br J Psychiatry 2006;189:124-31.

[72] Leverich GS, Altshuler Ll, Frye Ma, et al. *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;163:232-9.

[73] Post Rm, Altshuler LL, Frye MA, et al. *Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers*. Bipolar Disord 2001;3:259-65.

[74] Himmelhoch J, Mulla D, Neil J, et al. *Incidence and significance of mixed affective states in a bipolar population*. Arch Gen Psychiatry 1976;33:1062-6.

[75] Bottlender R, Rudolf D, Strauss A, et al. *Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients*. J Affect Disord 2001;63:79-83.

[76] Prien RF. NIMH report. *Five-center study clarifies use of lithium, imipramine for recurrent affective disorders*. Hosp Community Psychiatry 1984;35:1097-8.

[77] Prien RfF Caffey EM, Jr. *Long-term maintenance drug therapy in recurrent affective illness: current status and issues*. Dis Nerv Syst 1977;38:981-92.

[78] Prien RF, Klett CJ, Caffey EM, Jr. *Lithium carbonate and imipramine in prevention of affective episodes*. A comparison in recurrent affective illness. Arch Gen Psychiatry 1973; 29:420-5.

[79] 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;87:121-30.

[80] Keck PE, Jr, Corya SA, Altshuler LL, et al. *Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression*. J Clin Psychiatry 2005;66:611-6.

[81] Amsterdam JD, Shults J, Brunswick DJ, et al. *Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate*. Bipolar Disord 2004;6:75-81.

[82] Grunze H. *Treatment of acute bipolar depression: A European viewpoint*. The Journal of Bipolar Disorders: Reviews & Comentaries 2006;V:3.

[83] Schneck CD, Miklowitz DJ, Miyahara S, et al. *The prospective course of rapid-cycling bipolar disorder: findings from the step-bd*. Am J Psychiatry 2008.

[84] Truman CJ, Goldberg JF, Ghaemi SN, et al. *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 2007;68:1472-9.

[85] Bauer MS, Wisniewski SR, Marangell LB, et al. *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;67:48-55.

[86] Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. A*ntidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety*. J Clin Psychiatry 2010;71:372-80.

[87] Rouillon F, Serrurier D, Miller H et al. *Prophylactic efficacy of maprotiline on unipolar depression relapse*. J Clin Psychiatry 1991;52:423-31.

[88] Wittington C, Kendall T, Fonagy P, et al. *Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data*. The Lancet 2004;363:1341-5.

[89] Baker RW, Tohen M, Fawcett J, et al. *Acute dysphoric mania: treatment response to olanzapine versus placebo*. J Clin Psychopharmacol 2003;23:132-7.

90 Privitera MR, Maharaj K. *Mania from dose-related ziprasidone augmentation of an SSRI*. J Clin Psychiatry 2003;64:1393-4.

[91] Altshuler L, Kiriakos L, Calcagno J, et al. T*he impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review*. J Clin Psychiatry 2001;62:612-6.

[92] Altshuler L, Suppes T, Black D, et al. *Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up*. Am J Psychiatry 2003;160:1252-62.

[93] Altshuler LL, Post RM, Hellemann G, et al. *Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study*. J Clin Psychiatry 2009;70:450-7.

[94] O'Dowd A. *NICE issues new guidance to improve the treatment of bipolar disorder*. Bmj 2006;333:220.

[95] Chou JC, Zito JM, Vitrai J, et al. *Neuroleptics in acute mania: a pharmacoepidemiologic study*. Ann Pharmacother 2006;30:1396-8.