Treatment patterns in inpatients with bipolar disorder at a psychiatric university hospital over a 9-year period: focus on mood stabilizers

Michaela Walpoth-Niederwanger[a], Georg Kemmler[a], Heinz Grunze[b], Ulrike Weiß[a], Christine Hörtnagl[a], Robert Strauß[a], Imrich Blasko[a] and Armand Hausmann[a]

The increasing number of pharmacological treatment options for bipolar disorder seems to be paralleled by the number of evidence-based guidelines published previously. The aim of this study was to systematically examine the adherence to published guidelines and any change in prescription habits over time in a psychiatric hospital setting. This is a retrospective study of 531 bipolar in patients who were consecutively admitted to the Department for Psychiatry and Psychotherapy in Innsbruck. Their complete medical histories were evaluated for psychotropic medications, with a special focus on mood stabilizers (MSs). To compare the use of individual MSs or combinations with other psychotropic medications in two preselected observation periods (1999–2003 and 2004–07), we used Fisher's exact test. Overall, the proportion of patients receiving at least one MS increased significantly from 1999–2003 to 2004–2007 (74.1 vs. 83.1%, $P=0.011$). Among the individual MSs, valproate was used most frequently in both time periods, showing a significant increase ($P<0.001$). Prescriptions of quetiapine ($P<0.001$) and lamotrigine ($P=0.033$) increased significantly, carbamazepine showed a significant decrease ($P<0.001$). Prescriptions of lithium and olanzapine decreased without reaching significance. The significant increase in the prescription of MS reflects the increasing awareness and implementation of recent evidence-based medicine guidelines into clinical practice. Clinical decision making, usually made on the basis of individual clinical experience, should always be reevaluated using periodically updated evidence-based medicine guidelines. ***Int Clin Psychopharmacol*** **00:000–000**

International Clinical Psychopharmacology 2012, **00**:000–000

Keywords: bipolar disorder, evidence-based medicine, sex difference, mood stabilizers, treatment

[a]Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Innsbruck, Austria and [b]Institute of Neuroscience, Academic Psychiatry, Newcastle General Hospital, Newcastle University, Newcastle upon Tyne, UK

Correspondence to Michaela Walpoth-Niederwanger, MD, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria
Tel: +43 512 504 23636; fax: +43 512 504 3628;
e-mail: michaela.walpoth@i-med.ac.at

Received 17 January 2012 **Accepted** 6 June 2012

Introduction

Bipolar affective disorders are highly recurrent and frequently chronic. Bipolar disorders rank second among mental illnesses causing disability in working-age adults (Murray and Lopez, 1997). The rate of relapse, often leading to hospitalization, increases with the number of previous episodes (Kessing *et al*., 2004); therefore, preventing new episodes or at least lengthening the time to relapse is imperative.

The term mood stabilizer was first used by Litchfield (1960). In 1990, a first concept was published by Goodwin and Jamison in their textbook entitled 'Manic depressive illness'. The authors aimed to delineate a new group of drugs from antidepressants (ADs) (which might induce mania) and classical antipsychotics (AP) (which might induce depression). In the meantime, several other more stringent definitions were formulated; for example, by Bauer and Mitchner (2004). The authors proposed a 'bimodal' definition by which an agent is considered to be a mood stabilizer (MS) if it has efficacy in treating acute manic and depressive symptoms, and is effective in the prophylaxis of manic and depressive symptoms in bipolar disorder. Along with the classical drugs such as lithium and (with limitations) carbamazepine and valproic acid (VPA), there is also some evidence that atypical APs (aAPs) have mood-stabilizing properties in acute episodes, as well as in relapse prevention. However, the mood-stabilizing properties of aAP do not appear to be class specific; instead, they seem to be a substance-specific phenomenon. In terms of maintenance therapy, at this time, controlled data are available for olanzapine (Tohen *et al*., 2005), aripiprazole (Keck *et al*., 2007), quetiapine (Suppes *et al*., 2007; Vieta *et al*., 2008a, 2008b), long-acting risperidone (Macfadden *et al*., 2009; Quiroz *et al*., 2010) and ziprasidone as an adjunct to a classical MS (Bowden *et al*., 2010). MSs were divided by Rybakowski (2007) into two distinct groups: (a) valproate and lithium as first-generation MSs and (b) new APs and lamotrigine as second-generation MSs (Rybakowski, 2007).

0268-1315 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/YIC.0b013e328356ac92

Patients with a diagnosis of a bipolar disorder are most often prescribed a combination of psychopharmacological agents for mood stabilization (Lin *et al*., 2006; Baldessarini *et al*., 2008; Fountoulakis, 2010). Depending on the presence of a manic, depressive or mixed symptomatology, a specific pharmacological treatment needs to be considered. Currently, a broad portfolio of psychotropic substances is available to physicians; however, with the growing number of treatment options, clinicians now have the opportunity and likewise face the challenge of optimized and individualized treatments. To guide clinicians in this process and improve outcomes, evidence-based recommendations have been developed in the recent past.

The first guideline in the field of bipolar disorders was published by the American Psychiatric Association (1994), followed by updates in 2002 and 2004 (American Psychiatric Association, 2002, 2004). In 2002, the World Federation of Societies of Biological Psychiatry (WFSBP) published the first part of their guidelines on the topic of bipolar depression (Grunze *et al*., 2002), with an update in 2010 (Grunze *et al*., 2010). In 2003, the WFSBP guidelines for the treatment of mania (Grunze *et al*., 2003) were launched, with an update in 2009 (Grunze *et al*., 2009). Finally, in 2004, the WFSBP bipolar maintenance guideline was published (Grunze *et al*., 2004). In 2009, the British Association for Psychopharmacology (BAP) (Goodwin and Young, 2003) published guidelines in 2003, with an update in 2009 (Goodwin, 2009). In 2002, a report of the Texas Consensus Conference in 2000 (Suppes *et al*., 2002) was published, superseded by an update in 2005 named the 'Texas Implementation of Medication Algorithms' (TIMA) guidelines (Suppes *et al*., 2005).

In 2005, the Canadian Network for Mood and Anxiety Treatments (CANMAT) issued their first guidelines (Yatham *et al*., 2005); updates followed in 2007 (Yatham *et al*., 2006) and 2009 (Yatham *et al*., 2009). Since 2006, the UK National Institute for Health and Clinical Excellence (NICE) has made the NICE guidelines available online (National Institute For Health and Clinical Excellence, 2006). In general, these selected guidelines are based on an extensive review of the scientific literature, extracting randomized-controlled trials (RCTs) and other supportive evidence from large field studies and meta-analyses. Some guidelines, however, include expert opinion, when the literature provides insufficient or conflicting evidence, such as the BAP and TIMA guidelines. Others are based purely on clinicians' opinions obtained through polls, namely, the practice guidelines published by Sachs *et al*. (2000). Another approach, adopted by the TIMA, is to develop and test a therapeutic algorithm on the basis of scientific evidence and expert consensus opinions to standardize and improve clinical decision making.

Although users should assume that the evidence used in the guidelines is identical, there are some inconsistencies and discrepancies. This could be the result of a different impact assigned to RCTs vs. meta-analyses. The quality of meta-analyses can be quite heterogeneous and sometimes of questionable scientific value. Another difficulty when comparing guidelines might result from the impact of expert opinions, which differ by degrees depending on the methodology.

Despite these differences, published guidelines tend to converge on the level of first-line recommendations. More or less diverse treatment approaches can be found when second-line recommendations are considered and where the influence of empiric clinical decision making comes into play.

Recommendations for the treatment of mania and mixed states until 2007

Most of the guidelines available before 2007 and almost all guidelines published before 2003 consider lithium as the first-line option for the treatment of acute mania (Suppes *et al*., 2002; Goodwin and Young, 2003; Grunze *et al*., 2003; American Psychiatric Association, 2004; Yatham *et al*., 2005); however, valproate, carbamazepine and second-generation and third-generation APs such as olanzapine, quetiapine or risperidone, ziprasidone and aripiprazole are also recommended. Both monotherapies, as well as the combination of an MS with APs, are considered as options.

Because acute mixed states do not respond as favourably to lithium (Anderson, 2000) as euphoric mania, in these cases, all guidelines suggested the use of VPA (Grunze *et al*., 2002; Suppes *et al*., 2002; Goodwin and Young, 2003; American Psychiatric Association, 2004; Yatham *et al*., 2005) or APs such as olanzapine, risperidone, ziprasidone and aripiprazole, or a combination of MSs and APs (American Psychiatric Association, 2004; Yatham *et al*., 2005).

Recommendations for the treatment of depression until 2007

The use of ADs in the treatment of bipolar depression was still controversial. Although the switch-risk may have been overestimated in the past, ADs were still used with caution because of concerns of lack of efficacy and the risk of long-term affective destabilization. The BAP guidelines, however, suggested in mild depression or cases of previous mood instability with ADs either quetiapine or lamotrigine; recommendations for moderate cases included selective serotonin reuptake inhibitors (SSRIs) or other ADs (no tricyclic ADs) in combination with an antimanic medication. In moderate or severe cases, electroconvulsive therapy, including simplification of pre-existing polypharmacy, was recommended as a first-line treatment (Goodwin and Young, 2003). The CANMAT guidelines recommended lithium, lamotrigine or quetiapine, or a combination of lithium or VPA with an SSRI or bupropion (Yatham *et al*., 2005). The APA

recommended lithium or lamotrigine alone or in combination with an AD (SSRI) (American Psychiatric Association, 2004). The WFSBP guidelines preferred a combination of MSs (lithium, lamotrigine, VPA or carbamazepine) with an SSRI or bupropion (Grunze *et al*., 2002). Only NICE guidelines did not always recommend an MS; instead, they preferred an AD (SSRI) alone or in combination with an MS or an AP (National Institute of Health and Clinical Evidence, 2004). Despite the weak evidence, the TIMA guidelines preferred lithium as first-line monotherapy for acute bipolar depression. They suggested to optimize serum levels to more than 0.8 mmol/ml (Suppes *et al*., 2002). Otherwise, the authors recommended lamotrigine as a monotherapy; in the absence of premedication, they recommended an antimanic medication in combination with lamotrigine.

Recommendations for maintenance therapy until 2007

Until 2007, lithium was recommended for maintenance therapy, as a first-line treatment for most recent manic or mixed episodes in monotherapy, and in addition to VPA or novel APs (Suppes *et al*., 2002; Goodwin and Young, 2003; American Psychiatric Association, 2004; Grunze *et al*., 2004; Yatham *et al*., 2005). Alternatively, olanzapine, risperidone, quetiapine ziprasidone or aripiprazole was recommended for use. For primarily depressed patients, TIMA, BAP and WFSBP proposed lamotrigine as a first-line agent, with olanzapine and quetiapine being second-line alternatives (Suppes *et al*., 2002; Goodwin and Young, 2003; Grunze *et al*., 2004).

Most of the guidelines available before 2007 recommended monotherapy as the primary strategy. However, it had been well established through prescription rates that in clinical settings, patients with bipolar disorder treated with monotherapy represented a minority of about 20%. In addition, Lim *et al*. 2001 showed, in their sample of more than 1400 inpatients, that only one of three patients with nonpsychotic bipolar I disease was treated with a medication recommended by a guideline.

Given this low adherence to guidelines in other settings, the aim of this study was to evaluate the prescription habits at the Department of Psychiatry and Psychotherapy in Innsbruck. In addition, we examined a potential shift in prescription habits between 1999 and 2007. For simplification and to achieve meaningful numbers, we grouped gabapentin, lamotrigine, lithium, topiramate, (ox)carbamazepine, as well as olanzapine and quetiapine in combination as MSs.

Patients and methods

Patients aged 18 years or older with a diagnosis of bipolar affective disorders (ICD 9: 296.2, 296.3, 296.4, 296.5, 296.6; ICD 10: F 31.x) who were admitted as inpatients at the Department for Psychiatry and Psychotherapy for more than 7 days between 1999 and 2007 were included in this review. The study was approved by the local ethics committee.

On the basis of routine care patient charts, the complete medical histories were searched retrospectively for psychotropic medications, with a special focus on MSs. Incomplete forms were excluded from further analysis.

Prescription rates within the three diagnostic groups (manic, depressive and mixed episode) and their adherence to international guidelines published after 1999 were investigated.

Statistical methods

All statistical analyses are based on individual admissions (rather than individual patients), as patients' polarity of mood episode and their treatment modalities may change from one admission to the next. For a comparison of the three diagnostic groups with respect to sociodemographic and clinical variables, one-way analysis of variance, the Kruskal–Wallis test and the χ^2-test were used, depending on the variable type.

Taking into consideration the fact that a certain medication is often not given throughout the entire hospital stay, we calculated for each MS the relative amount of time a specific substance was administered. For simplification, we then dichotomized this variable and took into account only those medications that were used for at least 50% of hospital days. To compare the frequency of use of individual MSs or combinations with other psychotropic medications during the two time intervals (1999–2003 and 2004–2007), we used Fisher's exact test. The same test was used to compare prescription frequencies in male and female patients. In addition, logistic regression analysis was used to analyse the combined effect of patient characteristics and time (1999–2003 vs. 2004–07) on prescription frequencies.

Results

A total of 531 admissions with a diagnosis of bipolar disorder (ICD 9: 296.2, 296.3, 296.4, 296.5, 296.6; ICD 10: F 31.x) were recorded between 1999 and 2007. The mean age of the patients was 48.9 years; 68.1% were women. Patient characteristics, broken down by diagnostic group, are shown in Table 1.

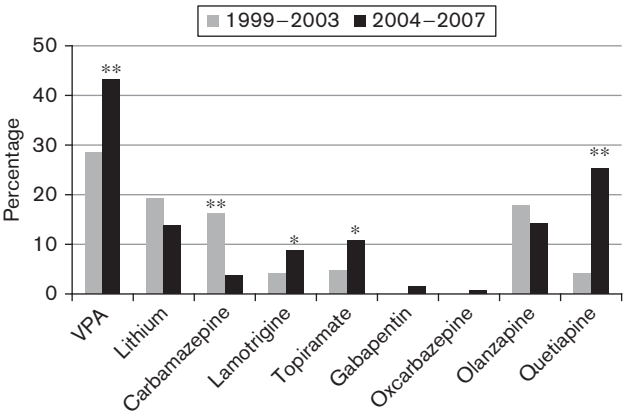
In the group of manic patients, the proportion of men was significantly higher than that in the mixed and depressed samples. Depressed patients were significantly older compared with the other two groups. Moreover, patients with a mixed episode had significantly shorter inpatient stays than manic or depressive patients. The distribution of the patient characteristics listed in Table 1 did not differ significantly for the total sample or for the diagnostic subgroups between the two time periods (1999–2003 and 2004–2007). Moreover, there were no significant differences between the two time periods with respect to the proportion of patients with substance abuse/dependence or those with psychotic symptoms.

Table 1 Characteristics of the 531 admissions with a diagnosis of bipolar disorder

Variables	Episode		
	Manic (*N*=212)	Depressive (*N*=239)	Mixed (*N*=80)
Sex			
Male (%)	42.5[a]	26.8	16.3
Female (%)	57.5	73.2	83.7
Age (mean±SD)	47.8±13.1	50.9[b]±13.8	46.8±14.8
Duration of illness (years, mean±SD)	19.3±12.2	17.7±12.8	16.2±12.1
Duration of stay (days, mean±SD)	36.7±32.4	39.2±29.9	26.0[c]±17.1

[a]Significantly more men in the manic episode group than in the other two groups (χ^2-test overall: $\chi^2=22.9$, *d.f.*=2, $P<0.001$; Fisher's exact test for manic vs. depressive and manic vs. mixed: $P<0.001$).
[b]Patients in the depressive episode group were significantly older than those in the other two groups (one-way analysis of variance: $F=4.6$, *d.f.*=2, $P=0.010$; depressive vs. manic: $t=2.38$, *d.f.*=1, $P=0.018$; depressive vs. mixed: $t=2.59$, *d.f.*=1, $P=0.010$).
[c]Mixed episode patients had significantly shorter inpatient stays than patients of the other two groups (Kruskal–Wallis test: $\chi^2=15.1$, *d.f.*=2, $P<0.001$; mixed vs. manic: Mann–Whitney *U*-test: $Z=3.08$, $P=0.002$, mixed vs. depressive: $Z=3.86$, $P<0.001$).

Fig. 1



Use of individual mood stabilizers at least 50% of the time during the inpatient stay (diagnostic groups pooled): comparison of 1999–2003 and 2004–2007. VPA, Valproic acid. *$P<0.05$; **$P<0.01$ (Fisher's exact test).

An overview of the MSs prescribed between 1999 and 2003 and from 2004 to 2007 is presented in Fig. 1. Overall, the proportion of patients receiving at least one MS increased significantly from 1999–2003 to 2004–2007. Among the individual MSs, VPA was used most frequently in both time periods, showing a significant increase of usage between observation periods [patients receiving VPA in 1999/2003 ($n=200$, 74.1%) vs. 2004/2007 ($n=217$, 83.1%); $P<0.001$]. In addition, we found a significant increase in patients receiving quetiapine [$n=11$ (4.1%) vs. $n=66$ (25.3%); $P<0.001$], topiramate [$n=13$ (4.8%) vs. $n=28$ (10.7%); $P=0.014$] and lamotrigine [$n=11$ (4.1%) vs. $n=23$ (8.8%); $P=0.033$] from 1999–2003 to 2004–2007. In contrast, prescription of carbamazepine [$n=44$ (16.3%) vs. $n=10$ (3.8%); $P<0,001$] showed a significant decrease over time. Lithium [$n=52$ (19.3%) vs. $n=36.4$ (3.3%)] and olanzapine [$n=48$ (17.8%) vs. $n=37$ (14.2%)] were also prescribed less frequently in 2004–2007 when compared with 1999–2003, although without reaching significance. Oxcarbamazepine ($n=2$) and gabapentin ($n=4$) were only prescribed during the second observation period.

A more detailed description of the prescribed MSs, according to diagnostic groups, is presented in Table 2. For the treatment of manic episodes, the use of VPA and quetiapine increased significantly between observation periods, whereas carbamazepine was prescribed significantly less frequently in 2004–2007 compared with 1999–2003. In patients with a depressive episode, the pattern was similar, with a significant increase in the use of VPA and quetiapine and a significant decrease in carbamazepine prescriptions. In addition, lamotrigine and topimarate were also prescribed significantly more frequently from 2004 to 2007. In mixed episodes, the use of quetiapine increased and the use of carbamazepine decreased significantly in 2004–2007 compared with 1999–2003. Logistic regression analysis showed that none of the observed changes in prescription frequencies between 1999–2003 and 2004–2007 were attributable to changes in the distribution of the patient sample with respect to sociodemographic or clinical variables (e.g. age, sex, duration of illness, psychotic symptoms or comorbid substance abuse).

With respect to polypharmacy, MSs were most often combined with AP in manic (64.1% in 1999/2003 vs. 78.0% in 2004/2007; $P=0.033$) and mixed episodes (57.5 vs. 60.0%; NS). A combination of MS plus AD medication (AD) was most prevalent in patients with a depressive episode, and this combination increased over time (50.4 vs. 67.0%; $P=0.012$). Both in manic and in depressive episodes, the proportion of patients receiving a combination of MS plus another MS, AD or aAP increased significantly from 1999–2003 to 2004–2007 (Table 3). Over the entire observation period, topiramate was found in combination with other MSs or quetiapine/olanzazine in 23 cases (4.3%). Topiramate as a monotherapy was found in 16 patients (manic episode: once topiramate in addition to an AP, once topiramate plus AD; depressive episode: 10 times topiramate plus AD, once topiramate plus AP; mixed episode: 3 times topiramate plus AP).

Again, these changes in prescription patterns were not attributable to changes in the distribution of the patient sample.

At discharge, the prescription patterns for MSs were very similar to those obtained during the stay in hospital and only lithium decreased significantly from 1999–2003 to 2004–2007 (Table 4).

The following significant differences were observed between male and female patients in the prescription

Table 2 Use of mood stabilizers by diagnostic group: 1999–2003 vs. 2004–2007[a]

Manic episode	*N* (%)		
	1999–2003 (*N*=103)	2004–2007 (*N*=109)	*P*-value
At least one MS	89 (86.4%)	93 (85.3%)	NS
VPA	35 (34.0%)	58 (53.2%↑)	0.006
Lithium	27 (26.2%)	23 (21.1%)	NS
Carbamazepine	17 (16.5%)	6 (5.5%↓)	0.014
Lamotrigine	3 (2.9%)	3 (2.8%)	NS
Topiramate	1 (1.0%)	7 (6.4%)	0.066
Olanzapine	24 (23.3%)	18 (16.5%)	NS
Quetiapine	2 (1.9%)	27 (4.8%↑)	<0.001
Depressive episode			
	1999–2003 (*N*=127)	2004–2007 (*N*=112)	
At least one MS	78 (61.4%)	93 (83.0%↑)	<0.001
VPA	31 (24.4%)	43 (38.4%↑)	<0.001
Lithium	15 (11.8%)	5 (4.5%)	0.059
Carbamazepine	17 (13.4%)	3 (2.7%↓)	0.004
Lamotrigine	7 (5.5%)	18 (16.1%↑)	0.010
Topiramate	7 (5.5%)	15 (13.4%↑)	0.044
Olanzapine	15 (11.8%)	15 (13.4%)	NS
Quetiapine	5 (3.9%)	27 (24.1%↑)	<0.001
Others[b]	0 (0.0%)	3 (2.7%)	NS
Mixed episode			
	1999–2003 (*N*=40)	2004–2007 (*N*=40)	
At least one MS	33 (82.5%)	31 (77.5%)	NS
VPA	11 (27.5%)	12 (30.0%)	NS
Lithium	10 (25.0%)	8 (20.0%)	NS
Carbamazepine	10 (25.0%)	1 (2.5%↓)	0.007
Lamotrigine	1 (2.5%)	2 (5.0%)	NS
Topiramate	5 (12.5%)	6 (15.0%)	NS
Olanzapine	9 (22.5%)	4 (10.0%)	NS
Quetiapine	4 (10.0%)	12 (30.0%↑)	0.048
Others[b]	0 (0.0%)	2 (5.0%)	NS

MS, mood stabilizer; VPA, valproic acid.
↑(↓) significantly higher (lower) in 2004–2007 than in 1999–2003 ($P<0.05$).
[a]Only mood stabilizers that were used more than 50% of the time during the hospital stay were counted.
[b]Gabapentin and oxcarbazepine.
NS, $P>0.1$.

of MSs: In manic episodes, lithium was more frequently used in men than in women (36.7 vs. 13.9%; $P < 0.001$), whereas carbamazepine was more frequently prescribed in women than in men (14.8 vs. 5.6%; $P = 0.043$). Male patients with a depressive episode received olanzapine more frequently than female patients (23.4 vs. 8.6%; $P = 0.044$). In mixed episodes, lithium was more frequently used in men than in women (53.8 vs. 16.4%; $P = 0.007$), whereas VPA was used more often in women than in men (34.3 vs. 0%; $P = 0.015$).

Discussion

All guidelines, with the exception of the 2006 NICE guidelines for the acute treatment of bipolar disorders, postulate that MSs should be started during acute treatment. This allows the substance to release its acute antimanic and antidepressive effects. It can also be continued as maintenance therapy. The significant increase in the prescription of MSs between the observation periods are in agreement with the changes in prescribing habits found by Centorrino *et al.* (2010). They underscore the increased awareness of the beneficial use of MSs in acute treatment.

Table 3 Use of two mood stabilizers simultaneously (at least 50% of the time during the hospital stay)

	N (%)		
	1999–2003 (*n*=270)	2004–2007 (*n*=261)	*P*-value
Two MS simultaneously	56 (20.7%)	94 (36.0%↑)	<0.001
VPA + another MS	25 (9.3%)	59 (22.7%↑)	<0.001
Lithium + another MS	21 (7.8%)	25 (9.6%)	NS
Carbamazepin + another MS	15 (5.6%)	6 (2.3%)	NS
VPA + Olz	13 (4.8%)	15 (5.8%)	NS
VPA + Que	3 (1.1%)	31 (11.9%↑)	<0.001
VPA + Li	6 (2.2%)	9 (3.4%)	NS
VPA + Carb	3 (1.1%)	2 (0.8%)	
Li + Olz	16 (5.9%)	3 (1.1%↓)	0.004
Li + Que	0 (0.0%)	15 (5.8%↑)	<0.001
Carb + Olz	4 (1.5%)	2 (0.8%)	NS
Carb + Que	2 (0.7%)	2 (0.8%)	NS

Carb, carbamazepine; Li, lithium; MS, mood stabilizer; Olz, olanzapine; Qu, quetiapine; VPA, valproic acid.

Manic and mixed episodes

Valproic acid and lithium

In our inpatient population, most of the manic patients were prescribed VPA, which was recommended during both observation periods as the first-line treatment in several guidelines (Suppes *et al.*, 2002; Goodwin and Young, 2003; Grunze *et al.*, 2003; American Psychiatric Association, 2004). Lithium ranked second over the entire 9-year period.

Lithium was the standard MS for years, but its use in Europe (Austria, Germany and Switzerland) has been decreasing; for example, in 1994–1999 vs. 2000–2004 (Wolfsperger *et al.*, 2007). An unchanged use of lithium was reported for England (2001–2009) (Gerrett *et al.*, 2010), the Netherlands (1996–2005) (Wilting *et al.*, 2008) as well as Sweden and Denmark (1981–2006) (Bramness *et al.*, 2009). Increasing prescription rates of lithium were reported from Spain (1985–2003) (Castells *et al.*, 2006), Norway (2004–2007) (Bramness *et al.*, 2009) and Italy (1994–1997) (Tognoni, 1999). The reasons for this pattern remain speculative, but are unlikely to be based on patient characteristics or a significant change in evidence base. Instead, they may be based on psychiatrist's attitudes towards new developments and possibly a different influence and lobbying effort of the pharmaceutical industry (Melander *et al.*, 2003). Carney and Goodwin (2005) also found a decrease in the use of lithium in North America and concluded that this is indicative of opinions rather than evidence.

A potential objective reason for the decrease in the use of lithium might be a more delayed antimanic effect. At the same time, the portfolio of rapid-onset antimanic drugs, such as VPA and novel APs, increased significantly. This may in part also be because of increasing economical pressure on hospitals to minimize the duration of inpatient stays.

Table 4 Mood stabilizers prescribed at discharge

	N (%)		
Manic episode			
	1999–2003 (*N*=103)	2004–2007 (*N*=109)	*P*-value
Any mood stabilizer	92 (89.3%)	92 (84.4%)	NS
VPA	40 (38.8%)	61 (56.0%↑)	0.014
Lithium	27 (26.2%)	22 (20.2%)	NS
Carbamazepine	17 (16.5%)	5 (4.6%↓)	0.006
Lamotrigine	4 (3.9%)	6 (5.5%)	NS
Topiramate	2 (1.9%)	5 (4.6%)	NS
Olanzapine	21 (20.4%)	18 (16.5%)	NS
Quetiapine	5 (4.9%)	23 (21.1%↑)	<0.001
Depressive episode			
	1999–2003 (*N*=127)	2004–07 (*N*=112)	
Any mood stabilizer	91 (71.7%)	97 (86.6%↑)	0.007
VPA	35 (27.6%)	47 (42.0%↑)	0.021
Lithium	17 (13.4%)	6 (5.4%↓)	0.047
Carbamazepine	22 (17.3%)	7 (6.3%↓)	0.010
Lamotrigine	9 (7.1%)	22 (19.6%↑)	0.006
Topiramate	8 (6.3%)	15 (13.4%)	0.079
Olanzapine	19 (15.0%)	16 (14.3%)	NS
Quetiapine	3 (2.4%)	31 (27.7%↑)	<0.001
Others[a]	0 (0.0%)	4 (3.6%)	NS
Mixed episode			
	1999–2003 (*N*=40)	2004–07 (*N*=40)	
Any mood stabilizer	32 (80.0%)	34 (85.0%)	NS
VPA	13 (32.5%)	15 (37.5%)	NS
Lithium	8 (20.0%)	8 (20.0%)	NS
Carbamazepine	10 (25.0%)	1 (2.5% ↓)	0.007
Lamotrigine	1 (2.5%)	1 (2.5%)	NS
Topiramate	5 (12.5%)	5 (12.5%)	NS
Olanzapine	9 (22.5%)	4 (10.0%)	NS
Quetiapine	2 (5.0%)	13 (32.5%↑)	0.003
Others[a]	0 (0.0%)	2 (5.0%)	NS

↑ (↓), significantly higher (lower) in 2004–2007 than in 1999–2003 ($P<0.05$); VPA, valproic acid.
[a]Only mood stabilizers that were used more than 50% of the time during the hospital stay were counted.
AQ1 [b]Gabapentin and oxcarbazepine.
NS, $P>0.1$.

A potential scientific reason for the increased use of valproate is the rapid onset of action combined with a wide safety margin. There is consistent evidence that valproate is an efficacious treatment for acute mania. A rapid VPA titration scheme named 'VPA loading' has been reported to be safe and well tolerated (Hirschfeld *et al*., 1999). However, VPA also harbours a potential risk of embryonic malformation and polycystic ovaries (Joffe *et al*., 2006).

Olanzapine

Olanzapine, an approved and recommended substance for the treatment of acute mania (Vieta *et al*., 2008a), was prescribed in 19.8% of manic episodes. Evidence suggests that valproate may be less effective in reducing manic symptoms than olanzapine (Tohen *et al*., 2008), but might cause less sedation. A recent study found that olanzapine has superior efficacy to lithium in the acute treatment of patients with bipolar mania. However, adverse events, such as GI side effects, dizziness, somnolence or restlessness, were experienced by a higher number of patients taking olanzapine than lithium (Niufan *et al*., 2008). A recent Cochrane database review by Cipriani *et al*. (2010) reports that olanzapine may prevent further manic episodes in patients who have responded to olanzapine during an index manic or mixed episode and who have not previously shown a satisfactory response to lithium or valproate. Given the solid scientific evidence both for the treatment of mania and the prevention of new manic episodes, olanzapine appears to be underutilized in comparison with other substances, especially valproate, in our sample. A potential reason for this may be uncertainty among doctors on the impact of metabolic changes associated with olanzapine (Newcomer, 2007).

Quetiapine

On comparing the years 1999–2003 and 2004–2007, it was found that the use of quetiapine increased from 4.9 to 24.8% in manic patients. This could be partially due to the formal approval for use in mania by Austrian authorities' in March 2004. The previous use of quetiapine to combat manic or psychotic symptoms in bipolar disorder was off label. The recent WFSBP guidelines (Grunze *et al*., 2004) confer a lower recommendation grade to the use of quetiapine in the treatment of mania compared with aripiprazole, risperidone and ziprasidone. It has been argued that the weaker dopamine D2 receptor blockade results in inferior antimanic properties.

The observed increase in the use of quetiapine in acute mania is in agreement both with guideline recommendations and with scientific evidence. In an international multicentre study comparing quetiapine with lithium and placebo, quetiapine showed a significantly higher response rate in mania than placebo. A significant difference from lithium was not apparent in this study, but was not formally tested (Bowden *et al*., 2005). Also, in combination with lithium or valproate, quetiapine significantly reduces manic symptoms (Tohen *et al*., 2003a; McIntyre *et al*., 2007; Sussman *et al*., 2007) and is also efficacious in maintenance therapy, for the prevention of both manic and depressive episodes (Vieta *et al*., 2008b; Suppes *et al*., 2009).

Carbamazepine and topiramate

The use of carbamazepine decreased significantly over the observation period of 9 years. There is strong evidence for the efficacy of carbamazepine in mania, but there are very few studies for other manifestations of bipolar disorder. The wider choice of antimanic medication, its adverse effect profile and pharmacokinetic interference with a wide range of drugs, many of them used in bipolar disorder, limit the use of carbamazepine in patients who have responded inadequately to other regimens (Bowden, 2009).

Topiramate showed a significant increase in prescription, irrespective of the current episode. Except for some open or single-blind studies (e.g. McElroy *et al*., 2000; Grunze *et al*., 2001; McIntyre *et al*., 2002), there is no evidence

base for its use in bipolar disorder and guidelines generally do not recommend it as a primary treatment for mood disorders. In fact, BAP, APA and NICE do not mention topiramate in their guidelines. CANMAT mentions topiramate as third-line therapy only in depression and as an adjunctive as a third-line option. WFSBP and TIMA do not consider topiramate to be a first line option when other treatments have failed. The increased use of topiramate is likely related to the striking problem of weight gain in bipolar disorder, as topiramate decreases appetite and induces weight loss (Woods *et al*., 2004).

The time to initial stabilization of an episode of bipolar disorders is generally the shortest with a manic episode and the longest with a mixed/cycling episode with the depressed episode in the middle (although almost as long as the mixed/cycling episode) (Kupfer *et al*., 2000). Our results show the opposite, with the shortest inpatient stay of patients in a mixed status. The endpoint of our individual observation period was the date of admission; therefore, some of our patients may have discontinued treatment without achieving remission.

Depressive episodes

Valproic acid and lithium

We observed a significant increase over time in depressed bipolar inpatients treated with a MS. VPA was the most frequently prescribed MS in our study population both in monotherapy and in combination with another MS. BAP, CANMAT and WFSBP guidelines mentioned VPA as the first-line treatment for depressive episodes only in combination with SSRI or bupropion. This is true for guidelines published during both observation periods. Only a few studies have shown a clinical benefit of VPA monotherapy in acute bipolar depression. Two recently published meta-analyses of VPA in acute depression by Smith *et al*. (2010) and Bond *et al*. (2010) were positive; however, the validity of these studies remains doubtful as their individual power is insufficient and the methodology varies. Except for a retrospective analysis of the only placebo-controlled VPA maintenance study, which shows lower discontinuation rates in patients on VPA compared with placebo when SSRI were added for breakthrough depression (Gyulai *et al*., 2003), there is no controlled evidence for the efficacy of the VPA/AD combination. As mentioned in most guidelines, the rationale for the combination of AD treatment with an MS in general, including VPA, is the prevention of treatment emergent affective switches.

The reduction in the use of lithium may be because of the emergence of new MSs, namely lamotrigine, and the well-described higher sensitivity of depressed patients to side effects, which are not rare with lithium. In addition, the accumulating evidence for the AD efficacy of some aAPs, especially quetiapine (Calabrese *et al*., 2005; Thase *et al*., 2006) and olanzapine (Tohen *et al*., 2003b), during the observation period 2004–2007 might have led to a change in prescription habits. The evidence base for lithium in bipolar depression is small and based mainly on older, underpowered studies (Gershon *et al*., 2009). In the only controlled study with sufficient power, lithium failed to separate from placebo, whereas the investigational substance quetiapine did (Young *et al*., 2010). American Psychiatric Association (2002) lists lithium or lamotrigine as a first-line option, and the TIMA 2005 lists lithium as a first-line option (optimizing the serum level) in the treatment of acute bipolar depression.

Quetiapine

Quetiapine showed a significant increase in prescription over time. As mentioned, this may indicate the accumulating evidence, although it was as late as 2006 when quetiapine first achieved a high ranking in bipolar depression guidelines (Yatham *et al*., 2009). It is noteworthy that the licensing in Austria for the treatment of acute bipolar depression was not until 2009.

In the light of missing data on the dose and particular time of intake, we suppose that in many cases, quetiapine was prescribed to calm patients (Datto *et al*., 2009). Despite quetiapine's sedative properties, current data do not appear to support its use as a first-line treatment for sleep complications (Wine *et al*., 2009). Cohrs *et al*. (2010), however, reported a clinically significant improvement in the amount and quality of sleep from the beginning of drug titration, which was consolidated with further administration of this medication and paralleled by a downregulation of the hypothalamic–pituitary–adrenal system after 3 weeks.

Olanzapine

There were no differences in the prescription rates of olanzapine over the years. In a randomized-controlled study, olanzapine's antidepressive properties started to separate from placebo at week 4. The decrease in the Montgomery Asberg Depression Rating Scale score, however, was mainly driven by olanzapine's effect on somatic symptoms, such as insomnia, loss of appetite, as well as irritability. Depressive core items improved significantly only when fluoxetine was combined with olanzapine (Tohen *et al*., 2006). As a consequence, olanzapine monotherapy had not achieved a priority ranking in current guidelines for bipolar depression. In addition, the evidence for olanzapine preventing new depressive episodes has, so far, been negative (Tohen *et al*., 2006; Smith *et al*., 2010).

Lamotrigine

Lamotrigine prescriptions for the acute treatment of bipolar depression showed a significant increase over time. This is in agreement with some guideline recommendations, mainly American Psychiatric Association (2002), but based on very weak evidence. Five of five

monotherapy studies in acute bipolar depression failed to separate from placebo on their primary outcome, the Hamilton Depression Rating Scale (Calabrese *et al*., 2008); only one (Montgomery Asberg Depression Rating Scale) succeeded on the secondary outcome (Calabrese *et al*., 1999). Only when all single-participant data of these studies were combined, which led to an artificial increase in the power post-hoc, did lamotrigine show a weak, but statistically significant acute AD effect (Geddes *et al*., 2009). In addition, the slow titration scheme might limit the clinical usefulness of lamotrigine as an acute AD treatment.

The evidence base is clearly different for the prevention of new depressive episodes with lamotrigine. A pooled data analysis of two positive placebo-controlled studies (Bowden *et al*., 2003; Calabrese *et al*., 2003) also supports the efficacy of lamotrigine as maintenance treatment (Goodwin *et al*., 2004).

Overall, the main use of lamotrigine in bipolar disorder is maintenance treatment to prevent depressive relapses. In this indication, lamotrigine is both licensed in many countries and overall recommended in the guidelines.

Sex differences in prescription patterns

Significantly more men than women received lithium, but there was no sex-difference in the use of VPA. This is a surprising finding, as there is so far no evidence for a difference in response to lithium between men and women. It is known that suicide attempt rates are higher among women than among men (Schmidtke *et al*., 1996; Nivoli *et al*., 2011). In addition, women prefer softer methods such as intoxications. The observed sex gap in our sample might be due to attempts to evade expected weight gain, as well as the increased possibility of birth defects. Although in the 1970s a high association of lithium intake and malformation was reported (especially Ebstein's anomaly), a re-evaluation in the 1990s (Cohen *et al*., 1994) showed a lower risk. However, adverse perinatal outcomes are more likely with higher lithium concentrations at delivery (Newport *et al*., 2005).

In our sample, more women than men used carbamazepine as an MS. The use of carbamazepine in women may lead to the relatively specific risk of spina bifida for the embryo in case of unexpected pregnancy, although this risk is smaller than that with the use of VPA (Jentink *et al*., 2010).

Our retrospective data do not clearly distinguish between nonpsychotic and psychotic depressive symptoms in bipolar disorder. We found that significantly more men were treated with olanzapine. Perhaps the men in our cohort tended to show more psychotic or dysphoric depressive symptoms, and therefore, the AP, mildly antidepressive and mood-stabilizing properties of olanzapine were taken into account when prescribing. Moreover, medication-associated weight gain may be more of an issue with women than men (Aichhorn *et al*. 2007).

Combination of mood stabilizers

Especially in long-term therapy, the BALANCE study indicated that both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than valproate monotherapy (Geddes *et al*., 2010). Although the use of valproate increased and the use of lithium decreased between the two observation periods, the combination of valproate and lithium showed no variation.

There has been an increase in add-on treatments, consisting of combinations of two MSs in general and in particular combinations with VPA, especially VPA and quetiapine. As Baldessarini and colleagues have pointed out in a study on polytherapy and adherence in the USA, polytherapy was used in one-third of bipolar patients initially. The most used initially prescribed MS was valproate in 2000–2004 (Baldessarini *et al*., 2008). At the time, intensive promotion by the pharmaceutical industry, as well as the marketing of valproic acid and second generation antipsychotics, provided strong competition for lithium (Baldessarini, 2010). During the second observation period, 36% of our patients received a combination of two MSs, irrespective of additional antidepressive, AP or sedative medication. In a recent study by Mojtabai and Olfson (2010), no increase in the prescription of MSs has been observed; however, there was an increase in polypharmacy involving AD and AP medications. The authors note the increasing risk of drug–drug interactions and question the quality of patient care. Findings from the STEP-BD study also showed that the use of traditional MSs is associated with fewer cotherapies (Goldberg *et al*., 2009).

Adherence to guidelines

To answer the question to what degree clinicians adhere to the evidence-based medicine (EBM) guidelines, we need to identify the prevailing opinion in these guidelines. There is a clear consensus supporting the use of MSs as a first-line treatment, especially the use of lithium and VPA in addition to aAPs, in the treatment of mania and mixed episodes. For the treatment of bipolar depression, we found different and diverging views. Whereas MSs are recommended by all mentioned guidelines, the use of ADs is restricted to SSRIs or bupropion, and to newer APs with antidepressive efficacy. Taking into account the tendency of clinicians to follow clinical routines, our data show a reasonable adherence to EBM guidelines. There is, however, scope for improvement.

Limitations

Our study has several limitations. Because of the retrospective and observational design, our participants were clinically diagnosed with bipolar disorder in the absence

of standardized interviews reflecting ICD 10 or DSM IV criteria. As such, there is a possibility of missing or wrongly including patients. Furthermore, we had to exclude incomplete charts, as there is no acceptable procedure to handle those missing data. Another limitation of our study is the predefined restriction of inclusion of only medication that was used for at least 50% of time. Thus, we cannot make firm conclusions on the short-term use of medication. However, there were no significant differences in prescription patterns while in hospital and at discharge, pointing towards some consistency in prescribing. Unfortunately, our data provided no information on response to treatment, but we assume that the possibility of discharge shows at least a partial remission in the majority of patients.

Conclusion

We observed a significant increase in MS prescription on comparing 1999–2003 and 2004–2007. The use of lithium decreased over time. In contrast, the prescription rates for quetiapine increased. During the second period, 25% of our bipolar patients were treated with quetiapine for more than 50% of the time.

In a future project, it might be interesting to assess the impact on prescription habits with a focus on the fact that a drug is approved by authorities, in comparison with mere recommendations by EBM guidelines.

In reality, patient populations, including ours, are diverse and different from participants in RCTs. This cannot be considered in EBM guidelines, and might explain some of the variance between clinical practice and evidence-based recommendations. Guidelines can support a clinical decision but will always be influenced by clinical experience, and very individual safety and tolerability issues. Guidelines prefer monotherapy as a first-line treatment, but most of our severely ill patients do not even achieve partial remission on monotherapy. Thus, it is also a task for guidelines to accept this clinical reality by making sensible recommendations for combination treatments. Clearly, further research is required to evaluate the efficacy, tolerability and safety of combining medications to achieve similar high levels of evidence. This already exists for some monotherapies.

Acknowledgements

Medical writing support was provided by Dora Kleis.

Conflicts of interest

H.G.: Advisory boards and speaker bureau for the last 3 years: Astra Zeneca, BMS-Otsuka, Cephalon, Gedeon Richter, Lilly, Lundbeck, Roche, Organon, UBS. A.H.: Advisory boards and speaker bureau for the last 3 years: Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Lundbeck. For the other authors there are no conflicts of interest.

References

Aichhorn W, Whitworth AB, Weiss EM, Hinterhuber H, Marksteiner J (2007). Differences between men and women in side effects of second-generation antipsychotics. *Nervenarzt* **78**:45–52.

American Psychiatric Association (1994). Practice guideline for the treatment of patients with bipolar disorder. *Am J Psychiatry* **151**:1–36.

American Psychiatric Association (2002). Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* **159**:1–50.

American Psychiatric Association (2004). *American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders*. Arlington, VA: American Psychiatric Publishing Inc.

Anderson J (2000). On variability of effects for a metaanalysis of rheumatoid arthritis radiographic progression. *J Rheumatol* **27**:540–542, discussion 542–543.

Baldessarini R, Henk H, Sklar A, Chang J, Leahy L (2008). Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv* **59**:1175–1183.

Baldessarini RJ (2010). Commentary: the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study. *Bipolar Disord* **12**:669–672.

Bauer MS, Mitchner L (2004). What is a 'mood stabilizer'? An evidence-based response. *Am J Psychiatry* **161**:3–18.

Bond DJ, Lam RW, Yatham LN (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 CL (2009). Anticonvulsants in bipolar disorders: current research and practice and future directions. *Bipolar Disord* **11 (Suppl 2)**:20–33.

Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, *et al.*; Lamictal 606 Study Group (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**:392–400.

Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, *et al.* (2005). A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* **66**:111–121.

Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M (2010). Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* **71**:130–137.

Bramness JG, Grøholt B, Engeland A, Furu K (2009). The use of lithium, valproate or lamotrigine for psychiatric conditions in children and adolescents in Norway 2004–2007 – a prescription database study. *J Affect Disord* **117**:208–211.

Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD (1999). A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* **60**:79–88.

Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, *et al.*; Lamictal 605 Study Group (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* **64**:1013–1024.

Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, *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 JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, *et al.* (2008). Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* **10**: 323–333.

Carney SM, Goodwin GM (2005). Lithium – a continuing story in the treatment of bipolar disorder. *Acta Psychiatr Scand* **Suppl**:7–12.

Castells X, Vallano A, Rigau D, Pérez J, Casas M, Capellà D (2006). Trends in lithium prescription in Spain from 1985 to 2003. *J Affect Disord* **91**: 273–276.

Centorrino F, Ventriglio A, Vincenti A, Talamo A, Baldessarini RJ (2010). Changes in medication practices for hospitalized psychiatric patients: 2009 versus 2004. *Hum Psychopharmacol* **25**:179–186.

Cipriani A, Rendell J, Geddes JR (2010). Olanzapine in the long-term treatment of bipolar disorder: a systematic review and meta-analysis. *J Psychopharmacol* **24**:1729–1738.

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

Cohrs S, Gade K, Meier A, Jordan W, Falkai P, Rüther E, Rodenbeck A (2010). Quetiapine improves sleep disturbance in acute bipolar disorder: a case series. *Pharmacopsychiatry* **43**:154–155.

Datto C, Berggren L, Patel JB, Eriksson H (2009). Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release

quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. *Clin Ther* **31**:492–502.

Fountoulakis KN (2010). An update of evidence-based treatment of bipolar depression: where do we stand? *Curr Opin Psychiatry* **23**:19–24.

Geddes JR, Calabrese JR, Goodwin GM (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 JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, *et al.*; Balance Investigators and Collaborators (2010). Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* **375**:385–395.

Gerrett D, Lamont T, Paton C, Barnes TR, Shah A (2010). Prescribing and monitoring lithium therapy: summary of a safety report from the National Patient Safety Agency. *BMJ* **341**:c6258.

Gershon S, Chengappa KN, Malhi GS (2009). Lithium specificity in bipolar illness: a classic agent for the classic disorder. *Bipolar Disord* **11 (Suppl 2)**:34–44.

Goldberg JF, Brooks JO, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, *et al.* (2009). Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry* **70**:155–162.

Goodwin GM. Consensus Group of the British Association for Psychopharmacology (2009). Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* **23**:346–388.

Goodwin GM, Young AH (2003). The British Association for Psychopharmacology guidelines for treatment of bipolar disorder: a summary. *J Psychopharmacol* **17**:3–6.

Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, *et al.* (2004). A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* **65**:432–441.

Grunze HC, Normann C, Langosch J, Schaefer M, Amann B, Sterr A, *et al.* (2001). Antimanic efficacy of topiramate in 11 patients in an open trial with an on-off-on design. *J Clin Psychiatry* **62**:464–468.

Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, *et al.*; World Federation of Societies of Biological Psychiatry Task Force on Treatment Guidelines for Bipolar Disorders (2002). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: treatment of bipolar depression. *World J Biol Psychiatry* **3**:115–124.

Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, *et al.*; WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2003). The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders. Part II: Treatment of Mania. *World J Biol Psychiatry* **4**:5–13.

Grunze H, Kasper S, Goodwin G, Bowden C, Möller HJ. WFSBP Task Force on Treatment Guidelines for Bipolar Disorderss (2004). 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* **5**:120–135.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S (2009). The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* **10**:85–116.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. WFSBP Task Force On Treatment Guidelines For Bipolar Disorders (2010). The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* **11**:81–109.

Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, *et al.* (2003). Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* **28**:1374–1382.

Hirschfeld RM, Allen MH, McEvoy JP, Keck PE, Russell JM (1999). Safety and tolerability of oral loading divalproex sodium in acutely manic bipolar patients. *J Clin Psychiatry* **60**:815–818.

Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, De Jong-Van Den Berg L. EUROCAT Antiepileptic Study Working Group (2010). Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. *BMJ* **341**:c6581.

Joffe H, Cohen LS, Suppes T, Hwang CH, Molay F, Adams JM, *et al.* (2006). Longitudinal follow-up of reproductive and metabolic features of valproate-associated polycystic ovarian syndrome features: a preliminary report. *Biol Psychiatry* **60**:1378–1381.

Keck PE, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, *et al.*; Aripiprazole Study Group (2007). Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry* **68**:1480–1491.

Kessing LV, Hansen MG, Andersen PK (2004). Course of illness in depressive and bipolar disorders. Naturalistic study, 1994–1999. *Br J Psychiatry* **185**:372–377.

Kupfer DJ, Frank E, Grochocinski VJ, Luther JF, Houck PR, Swartz HA (2000). Stabilization in the treatment of mania, depression and mixed states. *Acta Neuropsychiatrica* **12**:110–114.

Lim PZ, Tunis SL, Edell WS, Jensik SE, Tohen M (2001). Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines. *Bipolar Disord* **3**:165–173.

Lin D, Mok H, Yatham LN (2006). Polytherapy in bipolar disorder. *CNS Drugs* **20**:29–42.

Litchfield HR (1960). Aminophenylpyridone, a new mood-stabilizing drug. *Arch Pediatr* **77**:133–137.

Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, Bossie C, *et al.* (2009). A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disord* **11**:827–839.

McElroy SL, Suppes T, Keck PE, Frye MA, Denicoff KD, Altshuler LL, *et al.* (2000). Open-label adjunctive topiramate in the treatment of bipolar disorders. *Biol Psychiatry* **47**:1025–1033.

McIntyre RS, Mancini DA, McCann S, Srinivasan J, Sagman D, Kennedy SH (2002). Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disord* **4**:207–213.

McIntyre RS, Konarski JZ, Jones M, Paulsson B (2007). Quetiapine in the treatment of acute bipolar mania: efficacy across a broad range of symptoms. *J Affect Disord* **100 (Suppl 1)**:S5–S14.

Melander H, Ahlqvist RJ, Meijer G, Beermann B (2003). Evidence based medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* **326**:1171–1173.

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

Murray CJ, Lopez AD (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* **349**:1498–1504.

National Institute of Health and Clinical Evidence (2004). *NICE clinical guideline 38 bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care*. London UK: National Institute of Health and Clinical Evidence; Available at: *www.nice.org.uk/CG038*.

National Institute For Health and Clinical Excellence (2006). Available at: *http://www.nice.org.uk/CG038*. AQ2

Newcomer JW (2007). Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry* **68 (Suppl 4)**:8–13.

Newport DJ, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN (2005). Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry* **162**:2162–2170.

Niufan G, Tohen M, Qiuqing A, Fude Y, Pope E, McElroy H, *et al.* (2008). Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *J Affect Disord* **105**:101–108.

Nivoli AM, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, *et al.* (2011). Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. *J Affect Disord* **133**:443–449.

Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V (2010). Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry* **68**:156–162.

Rybakowski JK (2007). Two generations of mood stabilizers. *Int J Neuropsychopharmacol* **10**:709–711.

Sachs GS, Koslow CL, Ghaemi SN (2000). The treatment of bipolar depression. *Bipolar Disord* **2**:256–260.

Schmidtke A, Bille-Brahe U, Deleo D, Kerkhof A, Bjerke T, Crepet P, *et al.* (1996). Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989–1992. Results of the WHO/EURO Multicentre Study on Parasuicide. *Acta Psychiatr Scand* **93**:327–338.

Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL (2010). Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. *J Affect Disord* **122**:1–9.

Suppes T, Dennehy EB, Swann AC, Bowden CL, Calabrese JR, Hirschfeld RM. Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder (2002). Report of the Texas Consensus Conference Panel on

medication treatment of bipolar disorder 2000. *J Clin Psychiatry* **63**: 288–299.

Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR. Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder (2005). The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* **66**: 870–886.

Suppes T, Kelly DI, Keck PE, McElroy SL, Altshuler LL, Mintz J, *et al.* (2007). Quetiapine for the continuation treatment of bipolar depression: naturalistic prospective case series from the Stanley Bipolar Treatment Network. *Int Clin Psychopharmacol* **22**:376–381.

Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Trial 127 Investigators (2009). Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry* **166**:476–488.

Sussman N, Mullen J, Paulsson B, Vågerö M (2007). Rates of remission/euthymia with quetiapine in combination with lithium/divalproex for the treatment of acute mania. *J Affect Disord* **100 (Suppl 1)**:S55–S63.

Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A. BOLDER II Study Group (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.

Tognoni G (1999). Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. Italian Collaborative Study Group on the Outcome of Severe Mental Disorders. *Eur J Clin Pharmacol* **55**: 685–690.

Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L, *et al.* (2003a). Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* **160**: 1263–1271.

Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, *et al.* (2003b). Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* **60**:1079–1088.

Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, *et al.* (2005). Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*. **162**:pp. 1281–1290.

Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, *et al.* (2006). Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry* **163**:247–256.

Tohen M, Vieta E, Goodwin GM, Sun B, Amsterdam JD, Banov M (2008). Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *J Clin Psychiatry* **69**:1776–1789.

Vieta E, Panicali F, Goetz I, Reed C, Comes M, Tohen M, Board EA (2008a). Olanzapine monotherapy and olanzapine combination therapy in the treatment of mania: 12-week results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) observational study. *J Affect Disord* **106**:63–72.

Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M (2008b). Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord* **109**:251–263.

Wilting I, Souverein PC, Nolen WA, Egberts AC, Heerdink ER (2008). Changes in outpatient lithium treatment in the Netherlands during 1996–2005. *J Affect Disord* **111**:94–99.

Wine JN, Sanda C, Caballero J (2009). Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. *Ann Pharmacother* **43**:707–713.

Wolfsperger M, Greil W, Rössler W, Grohmann R (2007). Pharmacological treatment of acute mania in psychiatric in-patients between 1994 and 2004. *J Affect Disord* **99**:9–17.

Woods TM, Eichner SF, Franks AS (2004). Weight gain mitigation with topiramate in mood disorders. *Ann Pharmacother* **38**:887–891.

Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, *et al.*; Canadian Network for Mood and Anxiety Treatments (2005). Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord* **7 (Suppl 3)**:5–69.

Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, *et al.*; Guidelines Group, CANMAT (2006). Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. *Bipolar Disord* **8**:721–739.

Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, *et al.* (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* **11**:225–255.

Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, *et al.*; EMBOLDEN I (Trial 001) Investigators (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.

AUTHOR QUERY FORM

LIPPINCOTT
WILLIAMS AND WILKINS

JOURNAL NAME: YIC
ARTICLE NO: 200342
QUERIES AND / OR REMARKS

QUERY NO.	Details Required	Author's Response
Q1	Please provider a link for the footnote 'b' given for the table '4'.	
Q2	Please provide title and accessed date for the Reference 'National Institute For Health and Clinical Excellence'	