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Research report

# Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009

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ABSTRACT

*Background:* Pharmacological treatment of bipolar depression is a complex and controversial issue, and its real-world practice remains largely unknown.
*Method:* Observational analysis of the pharmacotherapy of 2231 psychiatric inpatients with a current episode of bipolar depression. The study was based on cross-sectional prescription data from European psychiatric hospitals that had been repeatedly collected between 1994 and 2009 through the collaborative Drug Safety in Psychiatry (AMSP) program.
*Results:* Overall 81.3% of patients received antidepressants (AD) (7.8% monotherapy), 57.9% antipsychotics (AP), 50.1% anticonvulsants (AC), 47.5% tranquilizers, and 34.6% lithium (Li). Use over time was stable for AD, decreased for Li, and increased for AC, AP and tranquilizers. Pronounced increases were specifically observed for quetiapine, lamotrigine and valproate. Use of tricyclic AD decreased but its prevalence was still 11.8% in 2009. Venlafaxine was used by 19.5% in 2009. We also observed an increase of polypharmacy combining AD, AP, AC and Li. From 2006 to 2009 37.0% received concomitant treatment with three, and 6.4% even with all four of those drug classes.
*Limitations:* Observational cross-sectional study without follow-up or additional clinical information.
*Conclusions:* Monotherapy with antidepressants and any use of tricyclic AD and venlafaxine still has a considerable prevalence in bipolar depression, but this is controversial due to the reported risk of treatment emergent affective switches. Triple and quadruple therapy is not evidence-based but increasingly used in clinical practice. This may reflect an attempt to overcome treatment failure, and further studies should evaluate efficacy and safety of this common practice.



## 1. Introduction

Pharmacological treatment of bipolar depression is a complex and controversial issue (Baldessarini et al., 2010; Fountoulakis et al., 2011; Nivoli et al., 2011; Vieta et al., 2010). This is at first due to the fact that only more recent clinical trials on the treatment of depression differentiate between unipolar and bipolar depression. Whereas the use of antidepressants is well established in unipolar depression, their efficacy in bipolar depression is under dispute (Fountoulakis et al., 2008; Gijsman et al., 2004; Moller et al., 2001; Sachs et al., 2007). Recent evidence suggests that antidepressants, particularly if used as monotherapy, may have mood destabilizing properties and trigger manic episodes, named treatment emergent affective switches (TEAS), and may even induce rapid cycling courses (Ghaemi, 2008; Leverich et al., 2006; Post et al., 2006; Schneck et al., 2008). Lithium as an alternative, again,

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has been studied mostly in combined populations of unipolar and bipolar depression. In both groups, its efficacy as monotherapy in acute episodes has not been clearly established (Calabrese et al., 2003; Nivoli et al., 2011; Young et al., 2010). For anticonvulsants and antipsychotics several studies have been performed on selected populations with bipolar depression only. The anticonvulsant lamotrigine has subsequently been approved for the prevention of depressive episodes (Calabrese et al., 2003), but its use in acute bipolar depression remains controversial as four out of five placebo-controlled trials failed to demonstrate efficacy as monotherapy, and any efficacy may indeed be limited to patients with severe depression (Calabrese et al., 2008; Geddes et al., 2009; Nivoli et al., 2011). In fact, so far only two treatments have been approved for acute bipolar depression: the antipsychotic quetiapine is the only approved monotherapy (Calabrese et al., 2005; Thase et al., 2006), and the antipsychotic olanzapine plus the antidepressant fluoxetine is the only approved combination therapy (Tohen et al., 2003). Off-label use of other monotherapies and combinations involving antidepressants, antipsychotics, anticonvulsants and lithium may be common in clinical settings, but the prevalence of this practice has never been studied.

In the absence of more controlled clinical trials, several guidelines provide additional treatment recommendations for acute bipolar depression including algorithms for individual patients, but those also led to conflicting conclusions and recommendations (Nivoli et al., 2011). In their recent review of treatment guidelines for acute bipolar depression Nivoli and coworkers concluded that a consensus emerges at least on the recommendation of quetiapine as first-line treatment and the clear discouragement of antidepressant monotherapy (Nivoli et al., 2011). Furthermore, they also stated that further effort may be necessary in order to improve the implementation of guidelines in clinical practice, which remains largely unknown (Nivoli et al., 2011).

In light of this challenging controversy and largely unknown real-world practice of pharmacotherapy for bipolar depression, it is of particular interest to look at actual prescribing under natural conditions in clinical practice including trends for recent changes over time, and to compare the results with recommendations from guidelines and clinical trials. In this study we therefore investigated pharmacotherapy for bipolar depression in a large representative psychiatric inpatient population in routine clinical practice between 1994 and 2009.

## 2. Methods

### 2.1. Data source

For the current study we used prescription data that had been collected through the international Drug Safety in Psychiatry (AMSP) program. AMSP is an ongoing international multicenter drug safety program collecting data on pharmacotherapy and adverse drug reactions from psychiatric hospitals in a naturalistic setting since 1993. Its methods have been described in detail elsewhere (Engel et al., 2004; Grohmann et al., 2004). Briefly, AMSP consists of two principle data collections from 87 hospitals so far in Germany, Switzerland and Austria, and for some time also from one hospital each in Belgium and Hungary. The number of participating hospitals increased from 9 in 1994 to 51 in 2009. In a cross-sectional approach all participating hospitals survey psychiatric inpatients on two reference days per year. All drugs administered on these days are recorded along with the patients' age, gender and leading psychiatric diagnoses. Furthermore, severe adverse drug reactions that occur at these hospitals in association with psychopharmacological treatment are continuously reported and collected. For the current study we only used the cross-sectional AMSP dataset with prescriptions from more than 90,000 patients surveyed between 1994 and 2009. After we received the anonymized raw dataset from AMSP we conducted extensive reformatting including matching of ATC codes to all prescribed active substances (Haueis et al., 2011).

### 2.2. Study population and design

Within the AMSP dataset we selected all patients with a current episode of bipolar depression based on ICD-10 diagnostic codes F31.3, F31.4 and F31.5. For the time before 2001 we also included all patients with the corresponding ICD-9 code. Of note, ICD codes do not allow to differentiate between bipolar I and II disorders. For the resulting study population we analyzed all demographic information and drug prescriptions at the day of data collection.

The ethics committee of the Ludwig Maximilian University of Munich, the location of the AMSP main data center, had approved our analysis of the AMSP data with a waiver of authorization.

### 2.3. Data analysis

We used primarily descriptive statistics with presentation of results in tables and graphs as appropriate. Additional analyses with stratifications over calendar years addressed trends over time. The chi-square test was used for comparing changes in the proportion of patients with prescriptions of specific drugs or drug classes over two different time strata. However, the descriptive and non-hypothesis based nature of this study with multiple comparisons should be considered when interpreting the provided p-values. Data management, calculations, analyses, tables and graphs were done using STATA 11.2 for MacOS X (STATA Corporation, College Station, TX, USA) and SPSS 18 for MacOS X (IBM Corporation, Somers, NY, USA).

## 3. Results

Characteristics of the study population are presented in Table 1. We identified 2231 patients with a leading admission diagnosis of bipolar depression, 94.6% based on ICD-10 codes and only 5.4% on ICD-9 codes. More patients were included during the second half of the 16-year observation period (68.6%), and there were more female (62%) than male patients.

Prescribing trends for the major classes of psychotropic drugs used in the treatment of bipolar depression are shown in Fig. 1, including any drug use as well as exclusive monotherapy for each class. Of note, for this purpose we defined monotherapy as the use of either antidepressants *or* antipsychotics *or* lithium *or* anticonvulsants, but additional use

**Table 1**
Characteristics of the study population (N = 2231).

| Characteristics | Frequencies |
|---|---|
| Age in years, median (range) | 57 (19–108) |
| Gender, n (%) | |
| Female | 1383 (62.0) |
| Male | 848 (38.0) |
| Calendar year, n (%) | |
| 1994–1997 | 248 (11.1) |
| 1998–2001 | 453 (20.3) |
| 2001–2005 | 701 (31.4) |
| 2006–2009 | 829 (37.2) |
| Diagnosis, n (%) | |
| ICD-10: bipolar affective disorder | |
| Current episode mild or moderate depression (F31.3) | 740 (33.1) |
| Current episode severe depression without psychotic symptoms (F31.4) | 1092 (48.9) |
| Current episode severe depression with psychotic symptoms (F31.5) | 281 (12.6) |
| ICD-9: bipolar disorder, depressive episodes | 118 (5.4) |

of other psychotropic drugs (e.g. tranquilizers) or use of more than one drug *within* the respective class was allowed. Antidepressants constituted the most frequently prescribed drug class in bipolar depression. Their use remained approximately stable over time with 81.3% of all patients receiving at least one, and 18.7% even two antidepressants. Furthermore 57.9% of the patients received antipsychotics, 50.1% anticonvulsants, 47.5% tranquilizers and 34.6% lithium. Combination of even two antipsychotics or two anticonvulsants had a prevalence of 9.8% and 5.7%, respectively. Lithium use decreased over time from 44.8% for the time from 1994 to 1997 to 34.4% from 2006 to 2009 ($p = 0.003$). In contrast, we observed a pronounced increase for the use of the other three presented drug classes over time, from 40.3% to 67.3% for antipsychotics ($p < 0.001$), from 28.6% to 53.0% for anticonvulsants ($p < 0.001$), and from 33.9% to 51.4% for tranquilizers ($p < 0.001$) comparing the time from 1994 to 1997 vs. 2006 to 2009. Monotherapy played virtually no role for all drug classes except antidepressants. Overall 7.8% received antidepressants as monotherapy, with a decrease from 13.7% to 5.2% ($p < 0.001$) comparing the time from 1994 to 1997 vs. 2006 to 2009. Of further note, among 341 quetiapine users only 11 patients received quetiapine as monotherapy.

More detailed views at prescribing trends for subclasses of antidepressants and the most frequently used antipsychotics and anticonvulsants are provided in Fig. 2. Regarding antidepressants we observed a pronounced decrease for the use of tricyclics. This was contrasted by an approximately parallel increase for selective serotonin reuptake inhibitors (SSRI), serotonin noradrenalin reuptake inhibitors (SNRI), and noradrenergic and specific serotonergic antidepressants (NaSSA). Of note, the use of SNRI recently did not further increase, but in 2009 the SNRI venlafaxine remained the most frequently prescribed antidepressant, used by 19.5% of all patients, followed by mirtazapine (19.0%) and

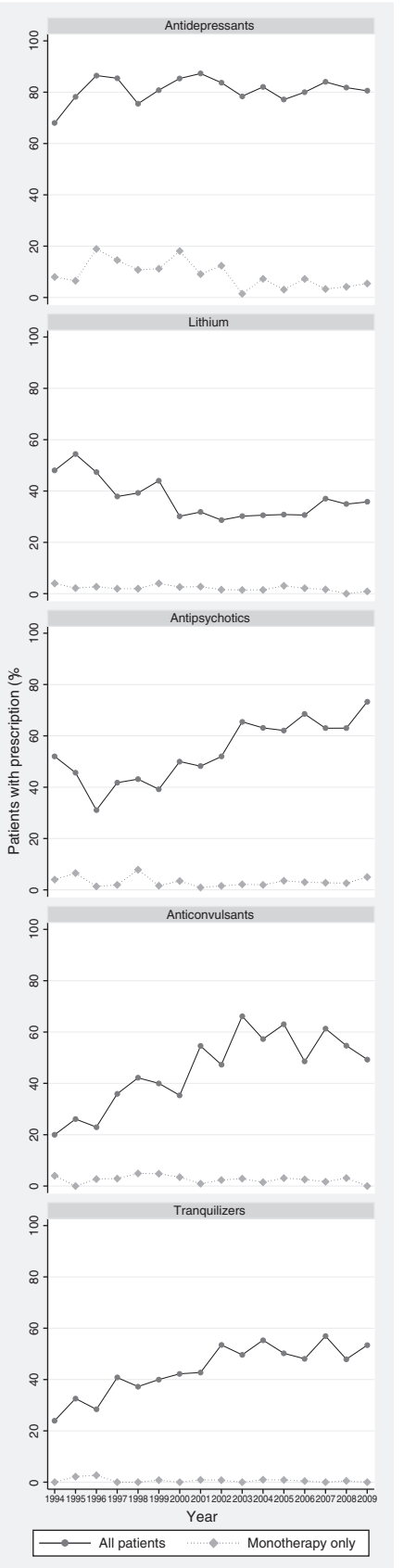



**Fig. 1.** Time trends for the prescription of psychotropic drug groups in bipolar depression presented as any use, and also as exclusive monotherapy defined as no use of any drug from other classes referring to antidepressants, lithium, antipsychotics and anticonvulsants.

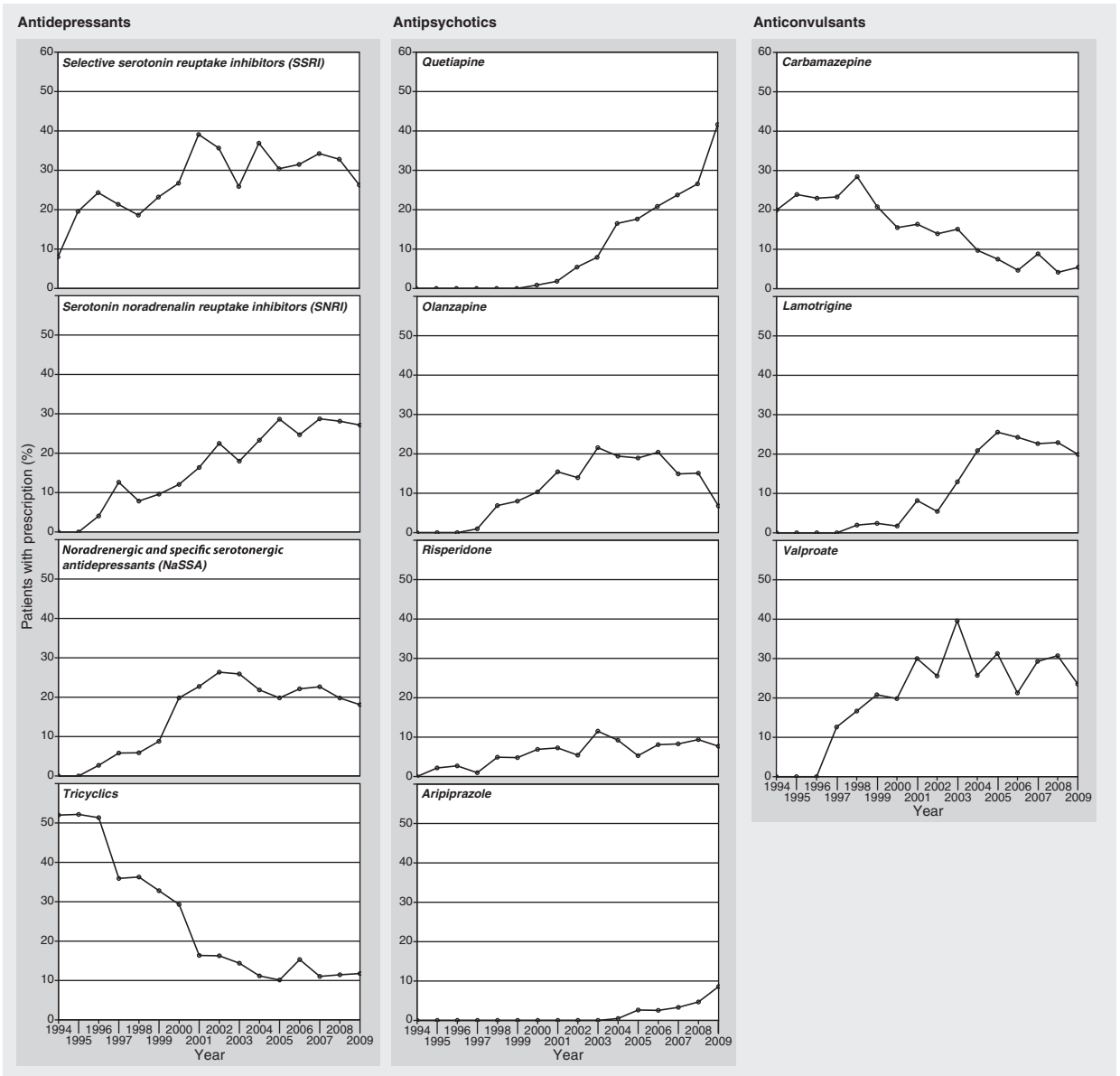



**Fig. 2.** Time trends for the prescription of the most frequently used antidepressants, antipsychotics and anticonvulsants in bipolar depression.

escitalopram (13.6%). Regarding antipsychotics quetiapine, olanzapine and risperidone accounted for 50.5% of all prescriptions within that class. Quetiapine use continuously increased ever since its first marketing. In 2009 it became the most frequently prescribed single substance, followed by lithium, which was the most frequently prescribed single substance in all previous years. In turn, the initial increase for olanzapine was reversed after the introduction of quetiapine. Risperidone and aripiprazole use increased as well, but they were prescribed much less frequently than quetiapine. For anticonvulsants carbamazepine, lamotrigine and valproate accounted for 89.4% of all prescriptions within that class. Carbamazepine use decreased over time, whereas one can see an increasing use of lamotrigine and valproate.

Overall trends for psychotropic polypharmacy regarding lithium, antidepressants, antipsychotics and anticonvulsants are presented in Fig. 3. Between 2006 and 2009 patients received on average 2.9 different substances belonging to those classes, compared to 2.1 between 1994 and 1997. Fig. 4 provides a more detailed analysis on polypharmacy for the four major drug classes used in the treatment of bipolar depression. For that purpose we defined double, triple and quadruple therapy as the concomitant use of *exactly* two, three or four of these drug classes, respectively, and use of several substances within one class was counted only once. Double therapy with lithium and antidepressants decreased from 22.6% to 6.5% ($p<0.001$) comparing the time from 1994 to 1997 vs. 2006 to 2009, when the most common double therapies had become

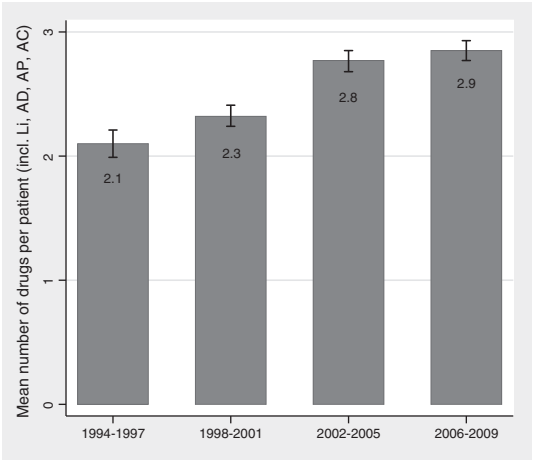



**Fig. 3.** Time trends for polypharmacy with psychotropic drugs showing mean additive counts for any antidepressants, antipsychotics, anticonvulsants and lithium per patient.

antidepressants plus antipsychotics (14.2%) or antidepressants plus anticonvulsants (13.5%). A remarkable increase was observed for triple therapies involving antidepressants, antipsychotics and anticonvulsants, which was the therapy of choice for 21.5% of all patients with bipolar depression between 2006 and 2009 ($p<0.001$ vs. 1994 to 1997). Another 11.7% received triple therapy with lithium, antidepressants and antipsychotics then. Finally, also maximum quadruple therapy with all four drug classes increased to 6.4% for the time between 2006 and 2009. Of further note, 302 patients received the antipsychotic olanzapine and 41 the SSRI fluoxetine, but only 5 patients received the specific combination of olanzapine plus fluoxetine.

## 4. Discussion

A large body of literature provides treatment recommendations for bipolar depression in the form of clinical trials, meta-analyses and guidelines (Baldessarini et al., 2010; Nivoli et al., 2011; Vieta et al., 2010). But treatment reality may differ considerably, and whereas there exists some pharmacoepidemiological data on bipolar disorders in general (Ghaemi et al., 2006; Goldberg et al., 2009; Levine et al., 2001; Lloyd et al., 2003; Paton et al., 2010), to our best knowledge there is no such data that specifically focuses on bipolar depression. The current study therefore investigated real-life prescribing behavior for bipolar depression in a large representative sample of European psychiatric inpatients over time. Indeed, we found not only several expected trends but also some remarkable discrepancies between real and recommended treatments.

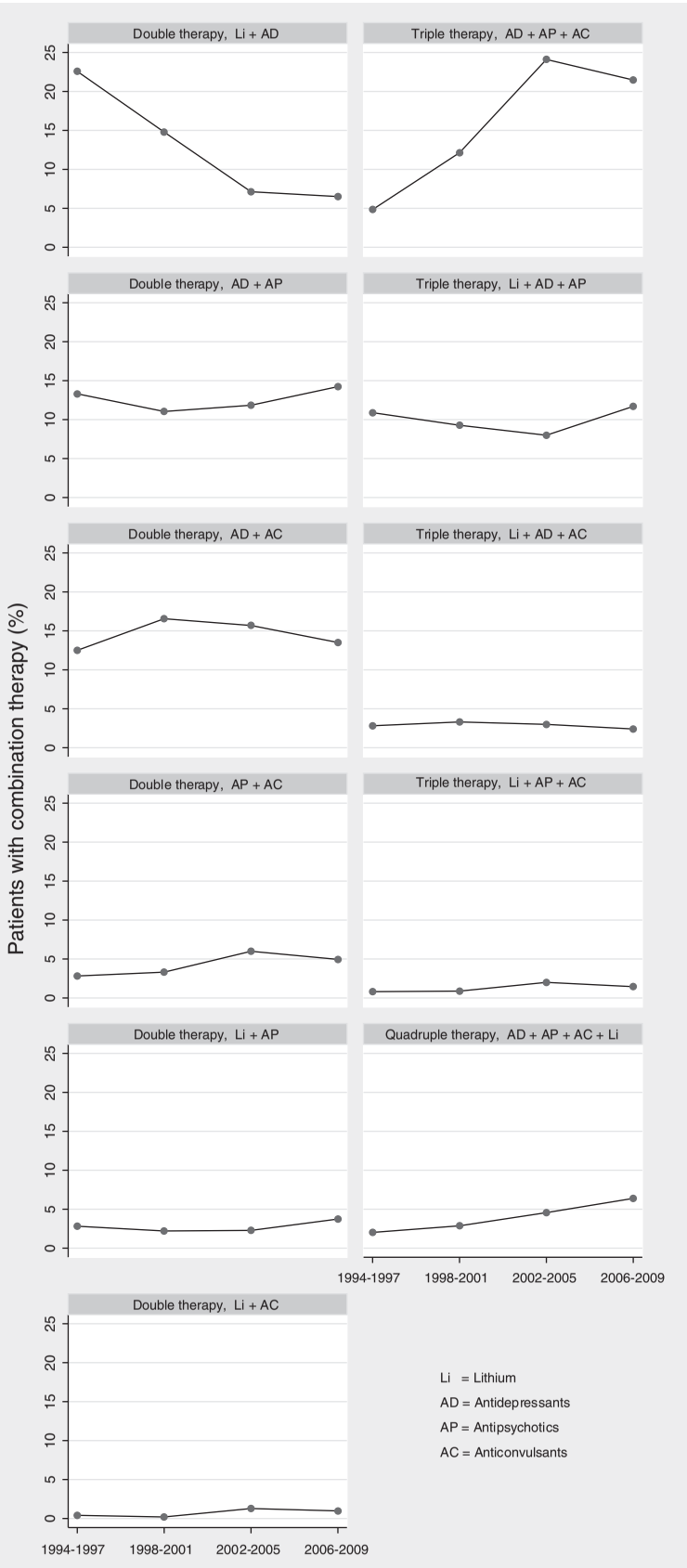
Although there is now a broad consensus that in bipolar depression antidepressants should only be given in combination with mood stabilizers due to the risk of treatment emergent affective switches (Ghaemi, 2008; Leverich et al., 2006; Post et al., 2006; Schneck et al., 2008) or should not be given at all due to a reported lack of efficacy (Sachs et al., 2007), we found that antidepressant use had an unchanged prevalence of about 80% and antidepressants therefore constitute by far the most frequently prescribed drug class in bipolar depression. And in particular, antidepressants are also used as monotherapy, which has been discouraged (Nivoli et al., 2011).

A more detailed look further reveals that the use of tricyclics decreased, contrasted by an increased use of SSRIs, SNRIs and NaSSAs. This is in line with general prescription trends for antidepressant use also for other indications (Stubner et al., 2010). However, the fact that even in 2009 more than 10% of bipolar patients received tricyclics and almost 20% venlafaxine raises concerns in light of their reported association with treatment emergent affective switches (Ghaemi, 2008; Leverich et al., 2006; Post et al., 2006; Schneck et al., 2008). If antidepressants are to be used in bipolar depression then rather SSRI or bupropion should be preferred according to various guidelines (Nivoli et al., 2011). On the other hand, a recent review concluded that serotonin reuptake does not seem to play a significant role in bipolar depression, whereas norepinephrine alpha-1 antagonism may be an important mechanism of action for the treatment of bipolar depression (Fountoulakis et al., 2011). Furthermore, bipolar I and bipolar II patients may differ in their risk of switching to (hypo) mania triggered by treatment (Leverich et al., 2006), and some authors even suggest stabilizing effects of SSRI monotherapy in patients with bipolar II disorder (Parker et al., 2006). Unfortunately, ICD diagnoses of our data did not allow further differentiating between treatments for bipolar I and II disorder.

Atypical antipsychotics are another recommended alternative (Nivoli et al., 2011), and in accordance with recent guidelines their use increased remarkably, particularly for quetiapine. Although quetiapine is the only approved monotherapy for bipolar depression, we only identified 11 patients with quetiapine monotherapy. However, one should consider that the studied population was limited to inpatients, where cases resistant to first-line monotherapy may account for the majority of patients. Before the establishment of quetiapine in bipolar depression olanzapine was the only approved antipsychotic in bipolar depression, although only since 2003 in the US and only in combination with the SSRI fluoxetine (Tohen et al., 2003). However, in our European population this specific combination had a negligible prevalence. It is also interesting to see that olanzapine use for bipolar depression in clinical practice increased immediately after its first marketing and was apparently counteracted by the introduction of quetiapine. Although risperidone is not mentioned in many guidelines its use constantly increased to about 10%. Similarly, aripiprazole prescriptions also increased to almost 10% although it is usually not recommended in bipolar depression (Yatham et al., 2009).

Anticonvulsants are used for their mood stabilizing effects in bipolar disorder. We observed a constant decrease in the use of carbamazepine, which may be related to its unproven efficacy in acute bipolar depression and possibly also to its potential to cause pharmacokinetic interactions via an induction of cytochrome P450 drug metabolizing enzymes. In contrast the use of valproate and lamotrigine has reached a prevalence of about 20%. Lamotrigine had been proposed as

**Fig. 4.** Time trends for combined treatment with specific psychotropic drug groups.


Double therapy, Li + AD
Triple therapy, AD + AP + AC
Double therapy, AD + AP
Triple therapy, Li + AD + AP
Double therapy, AD + AC
Triple therapy, Li + AD + AC
Double therapy, AP + AC
Triple therapy, Li + AP + AC
Double therapy, Li + AP
Quadruple therapy, AD + AP + AC + Li
Double therapy, Li + AC
Patients with combination therapy (%)
0
5
10
15
20
25
1994-1997
1998-2001
2002-2005
2006-2009
Li = Lithium
AD = Antidepressants
AP = Antipsychotics
AC = Anticonvulsants

a breakthrough in the treatment for bipolar depression in a guideline from 2004 (Calabrese et al., 2004), but later several previously unpublished negative studies and meta-analyses did not support its efficacy (Calabrese et al., 2008; Geddes et al., 2009). However, lamotrigine has an established role for the prevention of future depressive episodes (Baldessarini et al., 2010; Nivoli et al., 2011; Vieta et al., 2010) and might have been used for this purpose here.

Lithium is a well-established pharmacotherapy for bipolar disorder (Gershon et al., 2009; Paton et al., 2010), and although its use somewhat decreased over time we found it to be, in 2009 after quetiapine, the second most frequently prescribed single substance in bipolar depression. This may in part be due to the prophylactic efficacy of lithium. Several guidelines classify lithium as a first-line treatment in acute bipolar depression besides lamotrigine and quetiapine, respectively (Malhi et al., 2009; Yatham et al., 2009). And although a recent controlled study failed to support its efficacy in acute bipolar depression (Young et al., 2010), lithium is still recommended as a second-line choice in a most recent guideline (Grunze et al., 2010).

Besides prescribing trends for specific drug classes and substances, data on the frequency of polypharmacy for bipolar depression is one of the main findings of our study. Although olanzapine plus fluoxetine is the only FDA-approved combination therapy for bipolar depression, we found that the average combined number of any antidepressants, antipsychotics, anticonvulsants and lithium used per patient increased from about 2 to 3 over the past 15 years. Double therapy with antidepressants plus antipsychotics, or antidepressants plus anticonvulsants, both had – within the period of 2006 to 2009 – a prevalence of almost 15%, triple therapy with antidepressants plus antipsychotics plus anticonvulsants was prescribed to more than 20%, and even quadruple therapy with the further addition of lithium was increasing and with 6.4% not uncommon. A trend for psychiatric polypharmacy has previously also been reported for bipolar disorders in general (Goldberg et al., 2009), as well as for other indications such as psychoses or affective and anxiety disorders (Mojtabai and Olfson, 2010). Although there is a lack of appropriate studies that investigated the efficacy and safety of such extensive polypharmacy, a tendency has been described to continue adding more agents in an increasingly desperate attempt to provide relief in a suffering patient (Schatzberg et al., 2010). Indeed, also several guidelines and manuals recommend polypharmacy as part of escalation strategies in individual patients with bipolar depression in order to find the optimal therapy for an individual patient by a trial and error strategy (Fountoulakis, 2010; Nivoli et al., 2011; Schatzberg et al., 2010).

Some of the observed discrepancies between expert recommendations and real-life pharmacotherapy may also be due to the limitations of current randomized clinical trials as suggested by a recent systematic review (Spanemberg et al., 2011). The authors concluded that several articles on the pharmacological treatment of bipolar depression have methodological errors, biases and statistical simplifications, which complicate the extrapolation of the data to real-life settings. In addition, they also point out that many studies are sponsored by the pharmaceutical industry, and conflicts of interests may therefore influence their design, conduct, interpretation and overall validity for treatment in clinical practice.

Finally, some limitations of the presented study have to be mentioned. First, the used data source contains only repeated cross-sectional data, and we were therefore not able to follow the course of different therapies in individual patients over time. Consequently, change of treatments applying crossover strategies with increasing dose of a new drug and tapering of the previous treatment may have led to an overestimation of polypharmacy. However, even considering such a possible bias prevalences particularly for triple and quadruple therapies still remain remarkably high. Furthermore and as mentioned above our results apply to inpatients, which are expected to feature a higher proportion of treatment-resistant cases than an outpatient population.

Changes in prescription behavior over time might also be related to changes in the studied populations. Patients diagnosed as bipolar depressed in 1994 might be different to those in 2009. However, we found no change in the frequency of the diagnosis of bipolar depression, and no widening of the diagnosis of bipolar at the expense of unipolar depression was observed in our data. Also the change in the participating institutions and in their number over time may have influenced the results, but according to a recent study of the AMSP project it is unlikely that this would have influenced our results substantially (Konstantinidis et al., 2011). Finally, as in any observational database study misclassification of diagnoses and therapies is possible, but the extensive validation procedures applied over more than two decades to the AMSP database make this an unlikely source of bias.

In conclusion this observational study of pharmacotherapy for bipolar depression provides for the first time an intriguing picture of daily clinical practice over time and found some remarkable discrepancies between expert recommendations and treatment reality. Monotherapy with antidepressants and any use of tricyclic AD and venlafaxine still has a considerable prevalence in bipolar depression, but it is usually not recommended due to the reported risk of treatment emergent affective switches. Triple and quadruple therapy is not evidence-based but increasingly applied in clinical practice. This may reflect an attempt to overcome treatment failure, and further studies should evaluate efficacy and safety of this common practice.

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**Conflict of interest**

The authors report no financial or other relationship relevant to the subject of this article.

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