The use of (newer) antipsychotics in bipolar inpatients over a 17-year observation period

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Antipsychotics (AP) are commonly used in the treatment of bipolar disorder. They cover a broad spectrum of indications including acute psychotic, manic and depressive symptoms, and maintenance treatment. This study evaluates the changes in prescribing patterns of first-generation antipsychotics (FGA) and second-generation AP at Innsbruck University Hospital for the treatment of bipolar inpatients between 1999 and 2016. In this retrospective chart review, we included adult patients with a diagnosis of bipolar affective disorder (ICD 9: F296; ICD 10: F31) who were admitted as inpatients at the Department for Psychiatry and Psychotherapy between 1999 and 2016 for more than 7 days. The study was approved by the local ethics committee. The complete medical histories were searched retrospectively for the prescription of psychotropic medications at the time of discharge, with a special focus on APs. We found a significant increase in the use of atypical AP, mainly attributable to the prescription of quetiapine for all types of episodes, followed by aripiprazole for manic and as add-on therapy for depressive episodes. The prescription rate of clozapine decreased significantly. The prescription rate of FGA showed a small but not significant decrease for the treatment of manic and mixed episodes, and a significant decrease for depressive episodes. These trends apparently mirror in part the evidence base for the use of AP, but also illustrate that clinicians still appreciate the effectiveness of FGA despite their inferior tolerability profile. ***Int Clin Psychopharmacol*** **33:297–303**

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Introduction

Bipolar disorder (BD) is characterized by extreme and recurrent mood fluctuations, ranging from mania to severe depressive episodes (Goodwin and Jamison, 2007). Despite the marked increase in medications licensed for BD, treatment remains complicated, with inadequate response both in acute manic and depressive episodes as well as in maintenance treatment. Guidelines offer little advice on how to proceed when first-line treatment fails (Grunze, 2013a).

Mood stabilizers (MSs) such as lithium and valproate and first-generation antipsychotics (FGA) have been the preferred pharmacological treatments for decades, but more recently, newer or atypical antipsychotics (AAP) have established a firm evidence base and are increasingly being used in clinical practice. In a meta-analysis that examined medication use in 16 naturalistic studies between 1980 and 1997 and including 2378 BD patients, 84.7% of bipolar patients received typical antipsychotic (AP) agents either alone or in combination (Tohen *et al.*, 2001). In the AMSP project, which recorded pharmacotherapeutical trends between 1994 and 2009 in a European sample, 57.9% of bipolar depressive patients received APs (Greil *et al.*, 2012; Haeberle *et al.*, 2012). The high-affinity antagonism of FGAs to dopamine D2-receptor relates both to beneficial antimanic effects and also to disabling adverse effects (Tohen and Vieta, 2009), and potentially to mood destabilization (Tohen *et al.*, 2003). Treatment of acute mania with AAPs is associated with a 42% lower risk of a switch to depression than treatment with haloperidol (Goikolea *et al.*, 2013a). A previous meta-analysis had confirmed the high efficacy of haloperidol in the treatment of acute mania, also in comparison with several AAP (Goikolea *et al.*, 2013b); however, the lack of preventive properties against depression and the disadvantageous tolerability profile limit its usefulness across treatment phases (Berk and Malhi, 2011).

The first drugs largely devoid of extrapyramidal side effects were originally termed ‘atypical’ APs, but are now often called second-generation and third-generation APs. The use of AAPs in the management of adult BD has increasingly been adopted in clinical practice. The above-cited AMSP project observed, amongst others, an increasing prescription of AAP (mainly quetiapine) in the daily clinical routine of patients with bipolar depression (Greil *et al.*, 2012; Haeberle *et al.*, 2012). Some authors define the introduction of AAPs as a milestone in the

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treatment of BD (Fountoulakis *et al.*, 2017a). This statement is also supported by recent updates of major guidelines [NICE (National Collaborating Centre for Mental Health, 2014), CANMAT (Yatham *et al.*, 2013), CINP (Fountoulakis *et al.*, 2017b), WSFBP (Grunze *et al.*, 2009; Grunze *et al.*, 2010; Grunze *et al.*, 2013b), and British Association for Psychopharmacology (Goodwin *et al.*, 2016)] for the treatment of BD. For example, the NICE guideline recommends olanzapine, risperidone, or quetiapine as the first-line treatment for manic episodes and quetiapine, fluoxetine, and/ or olanzapine as the first-line treatment for depressive episodes.

Arguments for using AAP as first-line options in the treatment of BD include their lower switch risk to depression (Goikolea *et al.*, 2013a) and their comparable efficacy and better tolerability profile than FGA (Nivoli *et al.*, 2012). AAP are also promoted for the treatment of bipolar depression (Cruz *et al.*, 2010; Nivoli *et al.*, 2011). However, only olanzapine, alone or in combination with fluoxetine, quetiapine and lurasidone are approved by the US Food and Drug Agency for the treatment of bipolar depression, whereas only quetiapine is approved for treatment in countries regulated by the European Medicines Agency, including Austria. However, the relative lack of long-term experience and data, at least compared with lithium and FGAs, and especially the potential of metabolic adverse events leave many clinicians critical of these recommendations.

Combination strategies (also termed polypharmacotherapy) are commonly used in clinical practice to achieve maximum MS for bipolar illness (Solomon *et al.*, 1996; Frye *et al.*, 2000). The literature on combination strategies is confusing and sometimes contradictory in its use of language of the term assigned for the type of combination strategy (Altshuler *et al.*, 2003). We define two types of polypharmacotherapy: combination of two AP and augmentation strategies of AP with MSs or antidepressants (ADs).

The aim of this retrospective chart review is to evaluate the prescription of FGA and AAP in monotherapy as well as combination strategies in daily clinical routine at Innsbruck University Hospital for the treatment of bipolar inpatients over a 17-year period from 1999 to 2016. We hypothesized that there were significant changes in prescribing patterns, with an increase in AAP prescriptions and a decreased use of FGA for all kinds of episodes (acute manic, mixed, and bipolar depressive episode) reflecting the evidence base and guideline recommendations.

Patients and methods

Patients

Patients aged 18 years or older with a diagnosis of bipolar affective disorders (ICD 9: 296.x; 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 2016 were included in this study. The study was approved by the local ethics committee.

Medication

On the basis of routine care patient charts, the complete medical histories were evaluated retrospectively for the use of psychotropic medications at dismissal, with a special focus on APs. Incomplete forms were excluded from further analysis. Prescription rates within the three diagnostic groups (manic, depressive, and mixed index episode) were investigated over 17 years for three predefined intervals: 1999–2004, 2005–2010, and 2011–2016.

APs were clustered as low-potency AP, FGA, or AAP, the latter comprising of second-generation and third-generation APs. The low-potency AP group is characterized by a lower affinity to the D2 receptor and AP potency relative to their histaminergic and sedative properties. They were prescribed only for their sedative properties.

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 over time. To account for correlated observations in patients with several admissions, analyses with continuous dependent variables were carried out by linear mixed models and analyses involving binary dependent variables were carried out by generalized equation estimation (GEE) models with the binary response variable and the logistic link function. For both types of analyses, a first-order auto-regressive covariance structure was assumed. Before the analysis, all continuous variables were checked for deviations from normality and subjected to an appropriate 'normalizing' transformation (square root or logarithm) if required.

Linear mixed models were used to perform group comparisons with respect to age and duration of hospitalization; GEE models were used for comparisons in terms of sex. GEE models were also applied to compare the use of AP, MS, AD, or combinations of these between the three time intervals (1999–2004, 2005–2010, and 2011–2016). If a significant effect of the factor time was detected, subsequent pairwise comparisons of the individual time intervals (1999–2004 vs. 2005–2010, etc.) were performed on the basis of the Wald χ^2 statistic. As results might theoretically be affected by individuals with many readmissions, we carried out major analyses (comparisons of the use of medication types, for example, FGA or AAP, but not individual drugs) a second time excluding patients with ten or more admissions. However, no relevant changes in the findings were observed, that is, significances were always retained.

Results

Patients characteristics

A total of 715 patients with a diagnosis of BD (ICD 9: 296.x; ICD 10: F 31.x) were entered into the study, yielding a total of 1398 admissions. Most of the patients (87.4%) had one to three admissions during the observation period. Only a minority of patients had more than five admissions (39 or 5.4%) and very few patients had ten or more admissions (8 or 1.1%). Patient characteristics, broken down by diagnostic group, are shown in Table 1. For all types of episodes, the admission of women outnumbered the admission of men. The percentage of men was the highest in the manic episode group and the lowest in the mixed episode group.

The high proportion of admission for mixed states in women is noteworthy, which is a finding that has been described previously in other epidemiological studies (Arnold *et al.*, 2000). Depressed patients were significantly older compared with the other two groups. Moreover, patients with a depressive episode had a significantly longer duration of hospitalization than patients with a mixed episode.

Use of antipsychotics

The use of low-potency APs, FGA and AAP during the three time intervals (1999–2004, 2005–2010, and 2011–2016), broken down by diagnostic groups, is shown in Table 2. The prescription of sedating low-potency APs remained stable over time in manic patients, but showed a significant decrease in depressive and mixed episode patients. Medication with FGA declined significantly in the depressive ($P<0.001$) and mixed episode ($P=0.010$) groups.

The use of AAP showed a significant increase from 1999–2004 to 2005–2010 for all three types of episodes. In the manic and depressive episode group, this increase was followed by a nonsignificant decrease from 2005–2010 to 2011–2016. Amongst the individual AAPs, quetiapine showed the strongest increase of prescriptions in all three types of episodes, with only 9% low-dose quetiapine prescriptions. With prescription rates between 29 and 41% in 2005–2010 and between 21 and 42% in 2011–2016, it was the most frequently prescribed AP from 2005 onwards. Use of clozapine showed a significant decline in the manic ($P=0.014$) episode group. For the treatment of manic episodes, aripiprazole ($P\leq0.050$) and olanzapine ($P=0.021$) showed a significant increase in prescriptions. Aripiprazole also showed a significant increase ($P=0.008$) in the depressive episode group. The proportion of patients who had no AP at all did not change significantly in the manic group, whereas in the depressive sample, there was a significant reduction ($P=0.010$).

Table 1 Characteristics of the 1398 admissions with a diagnosis of bipolar disorder

	Episode		
Variables	Manic ($N=552$)	Depressive ($N=626$)	Mixed ($N=220$)
Sex [*n* (%)]			
Male	222 (40.2)[a]	154 (24.6)[b]	30 (13.6)
Female	330 (59.8)	472 (75.4)	190 (86.4)
Age (mean ± SD)	48.0 ± 13.9	51.9[c] ± 14.4	48.5 ± 14.2
Duration of inpatient stay (mean ± SD) (days)	31.7 ± 31.8	33.7[d] ± 28.4	26.8 ± 17.7

[a]Significantly higher proportion of men in the manic episode group than in the other two groups (Wald χ^2 statistic overall: $\chi^2=17.8$, $d.f.=2$, $P<0.001$, manic versus depressive: $P=0.004$, manic vs. mixed: $P<0.001$).
[b]Significantly higher proportion of men in the depressive than in the mixed episode group ($P=0.007$).
[c]Patients in the depressive episode group were significantly older than those in the other two groups (linear mixed models: $F=3.54$, $d.f.=2$, $P=0.029$; depressive versus manic: $P=0.024$; depressive vs. mixed, $P=0.017$).
[d]Patients in the depressive episode group had a significantly longer duration of hospitalization than patients of the mixed episode group (linear mixed models: overall $F=3.99$, $d.f.=2$, $P=0.019$; depressive vs. mixed: $P=0.006$).

Combination/augmentation strategies

The use of two AP in combination showed a significant increase from 1999–2004 to 2005–2010 in presently manic patients (from 7.0 to 20.5%, Wald $\chi^2=6.62$, $P=0.010$) and a significant decrease thereafter (20.5–11.6%, Wald $\chi^2=5.02$, $P=0.025$). In depressive episode patients, the proportion receiving two AP in combination increased steadily from 0% in 1999–2004 to 8.9% in 2011–2016 (Wald $\chi^2=4.95$, $P=0.026$). Mixed episode patients showed a pattern similar to those in the manic group, with a significant increase from 1999–2004 to 2005–2010 (0–15.9%, $\chi^2=6.01$, $P=0.014$), followed by a nonsignificant decrease to 9.1% in 2011–2016.

Augmentation strategies of AP with ADs or MS are shown in Table 3. In the manic episode sample, the most commonly used augmentation strategy was MS in addition to AAP, with no statistically significant changes over the three time intervals. In the depressive group, a significant reduction was observed for the augmentation with MS + FGA ($P=0.004$), MS + AD ($P<0.001$), and AD + FGA ($P<0.001$), accompanied by a significant increase in the combination of MS + AAP ($P<0.001$) and AD + AAP ($P=0.002$). In the mixed episode group, the combined prescription of MS + AAP was used most frequently (74.4% in the second time interval), also showing a significant increase over time.

Discussion

In our study, we investigated real-life prescribing habits in a population of bipolar inpatients. Our results confirm the increasing role of AAP as a treatment of choice in BD (Tohen *et al.*, 2001). We observed a significant increase in the prescription of AAP in the treatment of BD, with a peak in the observation period 2005–2010. These results confirm the results of previous North-American studies (Bulloch *et al.*, 2012; Pillarella *et al.*, 2012) in a European sample. However, in the 2011–2016 interval, we found a

Table 2 Use of antipsychotics: 1999–2004 versus 2005–2010 versus 2011–2016

(a) Manic episode

	n (%)			Statistics[a] overall comparison		1 vs. 2	1 vs. 3	2 vs. 3
	1999–2004 (*N* = 128)	2005–2010 (*N* = 166)	2011–2016 (*N* = 258)	Wald χ^2	*P*-value	*P*	*P*	*P*
Low potency AP	17 (13.3)	19 (11.4)	43 (16.7)	–[b]	NS	NS	NS	NS
First-generation AP	18 (14.1)	16 (9.6)	28 (10.9)	–[b]	NS	NS	NS	NS
Atypical AP	102 (79.7)	153 (92.2)$^{\uparrow}$	222 (86.0)$^{\uparrow}$	8.12	0.018	0.006	0.039	NS
Amisulpride	3 (2.3)	4 (2.4)	3 (1.2)	–[b]	NS	NS	NS	NS
Aripiprazole	–	8 (4.8)	28 (10.9)$^{\wedge}$	*3.84*	*0.050*	–[c]	–[c]	*0.050*
Asenapine	–	–	9 (3.5)	–[d]	–[d]			
Clozapine	26 (20.3)	9 (5.4)$^{\downarrow}$	23 (8.9)$^{\downarrow}$	*8.50*	*0.014*	*0.013*	*0.018*	NS
Olanzapine	29 (22.7)	23 (13.9)$^{\downarrow}$	69 (26.7)$^{\wedge}$	7.69	*0.021*	*0.041*	NS	*0.006*
Paliperidone	–	–	15 (5.8)$^{\wedge}$	–[d]	–[d]			
Quetiapine	8 (6.3)	49 (29.5)$^{\uparrow}$	54 (20.9)$^{\uparrow}$	*19.28*	*< 0.001*	*< 0.001*	*0.001*	NS
Risperidone	17 (13.3)	34 (20.5)	33 (12.8)$^{\vee}$	*5.36*	*0.069*	NS	NS	*0.026*
Ziprasidone	2 (1.6)	4 (2.4)	8 (3.1)	–[b]	NS	NS	NS	NS
Zotepine	21 (16.4)	44 (26.5)	0 (0.0)$^{\downarrow,\vee}$	*11.28*	*0.004*	NS	*0.001*	*0.001*
No AP	10 (7.8)	6 (3.6)	16 (6.2)	–[b]	NS	NS	NS	NS

(b) Depressive episode

	n (%)			Statistics[a] overall comparison		1 vs. 2	1 vs. 3	2 vs. 3
	1999–2004 (*N* = 158)	2005–2010 (*N* = 164)	2011–2016 (*N* = 304)	Wald χ^2	*P*-value	*P*	*P*	*P*
Low potency AP	66 (41.8)	44 (26.8)$^{\downarrow}$	50 (16.4)$^{\downarrow,\vee}$	25.60	< 0.001	< 0.001	< 0.001	0.015
First-generation AP	21 (13.3)	2 (1.2)$^{\downarrow}$	6 (2.0)$^{\downarrow}$	19.98	< 0.001	< 0.001	< 0.001	NS
Atypical AP	78 (49.4)	139 (84.8)$^{\uparrow}$	252 (82.9)$^{\uparrow}$	54.49	< 0.001	0.001	0.001	NS
Amisulpride	17 (10.8)	16 (9.8)	15 (4.9)$^{\downarrow}$	5.42	*0.067*	NS	*0.042*	*0.052*
Aripiprazole	–	12 (7.3)	50 (16.4)$^{\wedge}$	*7.05*	*0.008*	–[c]	–[c]	*0.008*
Asenapine	–	–	0 (0.0)	–[d]	–[d]			
Clozapine	1 (0.6)	6 (3.7)	16 (5.3)$^{\uparrow}$	*4.25*	NS (*0.119*)	NS	NS	*0.042*
Olanzapine	22 (13.9)	29 (17.7)	32 (10.5)$^{\vee}$	*7.41*	*0.025*	NS	NS	*0.012*
Paliperidone	–	–	1 (0.3)	–[d]	–[d]			
Quetiapine	10 (6.3)	51 (31.1)$^{\uparrow}$	128 (42.1)$^{\uparrow}$	*37.85*	*< 0.001*	*< 0.001*	*< 0.001*	*0.059*
Risperidone	15 (9.5)	12 (7.3)	20 (6.6)	–[b]	NS	NS	NS	NS
Ziprasidone	5 (3.2)	11 (6.7)	13 (4.3)	–[b]	NS	NS	NS	NS
Zotepine	8 (5.1)	8 (4.9)	1 (0.3)$^{\downarrow,\vee}$	*6.88*	*0.032*	NS	*0.009*	*0.021*
No AP	33 (20.9)	12 (7.3)$^{\downarrow}$	38 (12.5)	9.16	0.010	0.003	0.057	NS

(c) Mixed episode

	n (%)			Statistics[a] overall comparison		1 vs. 2	1 vs. 3	2 vs. 3
	1999–2004 (*N* = 50)	2005–2010 (*N* = 82)	2011–2016 (*N* = 88)	Wald χ^2	*P*-value	*P*	*P*	*P*
Low potency AP	12 (24.0)	14 (17.1)	6 (6.8)$^{\downarrow,\vee}$	7.05	0.029	NS	0.009	0.049
First-generation AP	8 (16.0)	5 (6.1)$^{\downarrow}$	9 (10.2)$^{\downarrow}$	9.29	0.010	0.003	0.019	NS
Atypical AP	33 (66.0)	77 (93.9)$^{\uparrow}$	71 (80.7)$^{\uparrow}$	13.51	0.001	0.001	0.041	0.062
Amisulpride	2 (4.0)	2 (2.4)	3 (3.4)	–[b]	NS	NS	NS	NS
Aripiprazole	–	6 (7.3)	8 (9.1)	–[b]	NS	–[c]	–[c]	NS
Asenapine	–	–	1 (1.1)	–[d]	–[d]			
Clozapine	6 (12.0)	4 (4.9)	2 (2.3)	–[b]	NS	NS	NS	*0.072*
Olanzapine	11 (22.0)	7 (8.5)$^{\downarrow}$	22 (25.0)$^{\wedge}$	*7.17*	*0.028*	*0.036*	NS	*0.009*
Paliperidone	–	–	1 (1.1)	–[d]	–[d]			
Quetiapine	4 (8.0)	34 (41.5)$^{\uparrow}$	30 (34.1)$^{\uparrow}$	*11.92*	*0.003*	*0.001*	*0.002*	NS
Risperidone	5 (10.0)	17 (20.7)	10 (11.4)	*5.63*	*0.060*	NS	NS	NS
Ziprasidone	0 (0.0)	8 (9.8)	2 (2.3)	*4.73*	*0.094*	NS	NS	NS
Zotepine	5 (10.0)	8 (9.8)	0 (0.0)$^{\downarrow,\vee}$	*5.44*	*0.066*	NS	*0.037*	*0.035*
No AP	6 (12.0)	3 (3.7)	7 (8.0)	–[b]	NS	NS	NS	NS

AP, antipsychotics.
[a]Generalized estimation equation (GEE) modeling.
[b]Wald $\chi^2 < 4.6$ (two *d.f.*) and hence $P > 0.1$.
[c]No statistical comparison with first time period possible as the medication was introduced after 2004.
[d]No statistical testing possible as the medication was introduced after 2010.
$^{\uparrow/\downarrow}$Significantly higher/lower than that in 1999–2004.
$^{\wedge/\vee}$Significantly higher/lower than that in 2005–2010, NS ($P > 0.1$).

modest decrease in AAP. We hypothesize that this might be related to a greater awareness of the long-term metabolic effects of some AAPs, but other mechanisms such as a decrease in the marketing activities of the producers might have also played a role that is difficult to quantify. Amongst the AAP, the use of quetiapine showed the biggest increased for all three types of episodes (Table 2a–c). This result is in line with the data

Table 3 Use of antipsychotics in augmentation with mood stabilizer and or antidepressants

(a) Manic episodes

	n (%)			Statistics[a]	
	1999–2004 ($N=128$)	2005–2010 ($N=166$)	2011–2016 ($N=258$)	Wald χ^2	*P*
MS overall	107 (83.6)	127 (76.5)	203 (78.7)	2.44	NS
MS + FGA	13 (10.2)	12 (7.2)	23 (8.9)	–[b]	NS
MS + AAP	89 (69.5)	120 (72.3)	174 (67.4)	–[b]	NS
MS monotherapy	7 (5.5)	4 (2.4)	12 (4.7)	–[b]	NS
MS + AD (without AP)	2 (1.6)	0 (0.0)	1 (0.4)	–[b]	NS
AD overall	9 (7.0)	14 (8.4)	25 (9.7)	0.52	NS
AD + FGA	1 (0.8)	0 (0.0)	0 (0.0)	–[b]	NS
AD + AAP	6 (4.7)	14 (8.4)	22 (8.5)	–[b]	NS
AD monotherapy	0 (0.0)	0 (0.0)	2 (0.8)	–[b]	NS

(b) Depressive episodes

	n (%)			Statistics[a]	
	1999–2004 ($N=158$)	2005–2010 ($N=164$)	2011–2016 ($N=304$)	Wald χ^2	*P*
MS overall	110 (69.6)	123 (75.0)	198 (65.1)	4.87	0.088
MS + FGA	14 (8.9)	2 (1.2)$^{\downarrow}$	6 (2.0)$^{\downarrow}$	10.98	0.004
MS + AAP	57 (36.1)	106 (64.6)$^{\uparrow}$	157 (51.6)$^{\uparrow,\vee}$	21.01	<0.001
MS monotherapy	2 (1.3)	2 (1.2)	10 (3.3)	–[b]	NS
MS + AD (no AP)	37 (23.4)	14 (8.5)$^{\downarrow}$	28 (9.2)$^{\downarrow}$	16.61	<0.001
AD overall	138 (87.3)	126 (76.8)$^{\downarrow}$	225 (74.0)$^{\downarrow}$	10.40	0.006
AD + FGA	18 (11.4)	0 (0.0)$^{\downarrow}$	3 (1.0)$^{\downarrow}$	23.43	<0.001
AD + AAP	67 (43.4)	105 (64.0)$^{\uparrow}$	187 (61.5)$^{\uparrow}$	12.85	0.002
AD monotherapy	16 (10.1)	7 (4.3)	8 (2.6)$^{\downarrow}$	9.57	0.008

(c) Mixed episodes

	n (%)			Statistics[a]	
	1999–2004 ($N=50$)	2005–2010 ($N=82$)	2011–2016 ($N=88$)	Wald χ^2	*P*
MS overall	35 (70.0)	63 (76.8)	76 (86.4)	4.93	0.085
MS + FGA	6 (12.0)	4 (4.9)	8 (9.1)	–[b]	NS
MS + AAP	22 (44.0)	61 (74.4)$^{\uparrow}$	61 (69.3)$^{\uparrow}$	12.53	0.002
MS monotherapy	2 (4.0)	0 (0.0)	6 (6.8)$^{\wedge}$	6.29	0.043
MS + AD (no AP)	5 (10.0)	2 (2.4)	1 (1.1)$^{\downarrow}$	5.75	0.056
AD overall	11 (22.0)	27 (32.9)	10 (11.4)$^{\vee}$	10.17	0.006
AD + FGA	1 (2.0)	0 (0.0)	0 (0.0)	–[b]	NS
AD + AAP	5 (10.0)	25 (30.5)$^{\uparrow}$	8 (9.1)$^{\vee}$	13.79	0.001
AD monotherapy	0 (0.0)	0 (0.0)	1 (1.1)	–[b]	NS

AD, antidepressants; AAP, atypical antipsychotics; AP, antipsychotics; FGA, first-generation antipsychotics; GEE, generalized equation estimation; MS, mood stabilizer; $P>0.1$, NS.
[a]Wald χ^2 value obtained from GEE analysis (overall comparison of the three time periods).
[b]$\chi^2<4.6$, corresponding $P>0.1$.
$^{\uparrow/\downarrow}P\leq0.05$, significantly higher/lower than that in 1999–2004.
$^{\wedge/\vee}P\leq0.05$, significantly higher/lower than that in 2005–2010.

from the AMSP project (Greil *et al.*, 2012; Haeberle *et al.*, 2012) and parallels the Food and Drug Agency and European Medicines Agency approval of quetiapine as monotherapy for acute manic and depressive episodes, as well as for maintenance treatment. Aripiprazole also showed a significant increase in the prescription rates in our study. Since the original approval in 2004 and the marketing for BD in 2009, the prescription rates of aripiprazole showed a significant increase in the manic ($P=0.050$) and depressive ($P=0.008$) episode group, although it is approved only for manic episodes and for the long-term prophylaxis of manic episodes. We assume that clinicians were aware of the positive results of the aripiprazole-add-on studies in unipolar depression, extrapolating the results to bipolar depression. Olanzapine use showed a significant increase ($P=0.006$) from 2005–2010 to 2011–2016, becoming the most frequently prescribed AAP (26.7%) in manic patients. In parallel, olanzapine also showed a significant increase ($P=0.009$) in the mixed episode group. The reasons for this may be complex: clinicians and patient satisfaction (Yen *et al.*, 2008), accumulated experience after several years of usage, generic price, and a solid evidence base for efficacy both in mania and in mixed states (Grunze *et al.*, 2009; Takeshima, 2017). The prescription rate of clozapine decreased significantly in the manic ($P=0.013$) episode sample. This may be related to the availability of more treatment options with lower risks and legal barriers.

However, we observed a significant increase in clozapine prescription in depressive episode patients from 0.6% in the first time interval to 5.3% in the last interval. We assume that this is a time effect as antidepressive augmentation of AD using AAP was just emerging at the turn of the century, and memories of the fatalaties due to non-monitored clozapine induced dyscrasias, was still fresh.

Although prescription of AAP was on the rise, we observed a decline in the use of FGAs. In manic and mixed episode patients, we observed a decrease in FGA use from 1999–2004 to 2005–2010, and a slight recovery between 2005–2010 and 2011–2016, all changes without statistical significance. With increasing economic pressure and the need to shorten the duration of hospitalization, the more rapid onset of the antimanic action of haloperidol (Goikolea *et al*., 2013b) becomes an important argument for initial FGA use. However, the depressive episode sample showed a statistically significant decrease in FGA prescriptions ($P < 0.001$). Both the greater side-effect burden and the better quality of evidence for AAP augmentation (Grunze *et al*., 2010) may explain the decrease in FGA prescriptions in depressive episodes.

Combination and augmentation strategies in bipolar patients are common (Greil *et al*., 2012; Haeberle *et al*., 2012), particularly in partial responders or refractory patients (Sachs *et al*., 2014). Patients with BD are treated with an average of 3–4 different types of psychotropic medications (Post *et al*., 2011; Kleimann *et al*., 2016). Our data confirm the increasing trend toward polypharmacy. Overall, an increase in the combined use of two APs over time was observed, reaching statistical significance in each of the diagnostic groups, except for the last observation period, where we observed a significant decrease within the manic sample. Augmentation strategies such as MS + AAP (69.5, 72.3 and 67.4%) did not change over time. Combining MS and AAP in mania is a strategy supported by evidence (Fountoulakis *et al*., 2017b). In patients with a depressive episode, we observed a statistically significant reduction ($P = 0.004$) in the combination of MS + FGA and of AD + FGA ($P < 0.001$). In the same patient sample, we also observed a significant increase ($P < 0.001$) in the use of the combination of MS + AAP, as well as a statistically significant increase ($P = 0.002$) in the use of the AD + AAP combination. These results may mirror the previously cited higher risk of causing depression by FGA and the better side-effect profile of AAPs.

So far, only a few studies have reported the results for mixed episodes separately from manic episodes. We found that MS + AAP is the most often prescribed combination in mixed-episode patients showing a significant increase over the time intervals. Our result is in line with a recently published guideline on the treatment of mixed episodes by the WFSBP (Grunze *et al*., 2018). The authors conclude that olanzapine (in mono- or combination treatment) appears to be the medication that covers most treatment scenarios and subgroups in mixed patients, albeit at a major long-term tolerability and safety cost. Furthermore, Takeshima (2017) confirmed that combination therapy could be more efficacious than monotherapy for the treatment of mixed states, and may be preferable at least in severe cases.

Limitations

Participants received a clinical diagnosis of BD in the absence of standardized interviews on the basis of 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 missing data. Another limitation of our study is the retrospective chart review design; there was no scope to follow up the patients. In addition, we recorded only medication at discharge. Thus, the study rather depicts the finally successful medication in contrast to an assessment of medication over the course of treatment. At the same time, this may constitute a strength of the study as it may provide indirect evidence of what kind of medication works best in real-world patients, and not just reflect marketing trends or other variables that may influence clinicians' first-choice treatment.

Conclusion

The results of our retrospective chart review confirm in a European inpatient sample prescribing trends observed previously in North-American study populations. Over time, AAP have by and large replaced FGAs, especially in bipolar depressed and mixed patients. In acute mania, there still seems to be a niche for the FGAs, hypothetically when a rapid onset of action becomes mandatory. Also in combination/augmentation treatment, AAPs have replaced FGA in the majority of patients. In general, treatment habits in this sample follow current scientific evidence and guidance, with slight modifications on the basis of the needs for clinical practice such as the continuous use of FGA in mania and the frequent combination treatments.

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Conflicts of interest

There are no conflicts of interest.

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