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Antipsychotic use in Northern Italian inter-episode bipolar disorder patients: considering both second- and first-generation agents

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Evidence supports increasing antipsychotic use in bipolar disorder, especially second-generation antipsychotics. However, data regarding first-generation antipsychotic contemporary use are limited. We studied 380 Northern Italian bipolar disorder inter-episode patients, grouped according to current antipsychotic use, stratified by bipolar subtype (BDI vs. BDII). Furthermore, we compared first-generation antipsychotic users vs. non-users. In our sample (n = 357), 81.8% were taking antipsychotics (74% second-generation antipsychotics, 24.1% first-generation antipsychotics), with antipsychotic use in BDI significantly more prevalent than in BDII (85.2% vs. 72.0%). Overall, antipsychotic users vs. non-users had higher rates of hypo/manic last episode, lifetime psychiatric hospitalization, psychosis, and current psychotropic use, but lower rates of anxiety disorder main comorbidity and current antidepressant use. First-generation antipsychotic use rates (30.3% in BDI vs. 6.5% in BDII) were associated with more frequently being unpartnered, having elevated first/last episodes, higher lifetime hospitalization, involuntary commitment, psychosis, and psychosocial rehabilitation rates, and more current psychotropic use, but lower Global Assessment Functioning scores and less current antidepressant use. Bipolar disorder patients had robust antipsychotic (second-generation antipsychotic > first-generation antipsychotic) use, consistently with previous reports. ~~FGAs~~ were still prescribed for a substantial group of patients, likely suffering from severe bipolar disorder. Prescriptions need to be monitored to assess their appropriateness and adherence to evidence-based recommendations. *Int Clin Psychopharmacol* XXX: 000–000 AQ2 **Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.**

International Clinical Psychopharmacology 2019, **XXX**:000–000

Keywords: antipsychotics, bipolar disorder, first-generation antipsychotics, second-generation antipsychotics AQ3

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Received 27 February 2019 **Accepted** 5 June 2019

Introduction

Pharmacological treatment is a fundamental part of overall bipolar disorder (BD) management~~,~~ and in the last two decades the advent of new treatment options with documented acute or longer-term efficacy has broadened BD therapeutic possibilities, extending them to a wide array of novel strategies aimed at better controlling acute symptoms, reducing severity, and preventing mood episode relapse/recurrence (Depp *et al.*, 2008), potentially decreasing clinical burden and healthcare resource use associated with BD (Vieta *et al.*, 2013).

Beyond lithium, which has been traditionally considered first-line as BD maintenance treatment (Rybakowski, 2014) and in America for acute mania (Suppes *et al.*, 2002; Goodwin and Young, 2003; Grunze *et al.*, 2003; ~~Young, 2003;~~ American Psychiatric Association, 2004; Yatham *et al.*, 2005), an increasing number of innovative treatments have recently received US Food and Drug Administration (US FDA) and International regulatory approval for BD treatment (Sachs and Thase, 2000; Baldessarini and Tarazi, 2005; Vieta *et al.*, 2011; Grunze *et al.*, 2013).

In case of inadequate response or tolerability with lithium, some anticonvulsant agents, most frequently valproate and less often carbamazepine, have been US FDA-approved for their monotherapy antimanic properties (Weisler *et al.*, 2006), whereas lamotrigine has been US FDA-approved as monotherapy for BD maintenance. Indeed, these advances have increasingly impacted clinical practice to date (Fenn *et al.*, 1996; Citrome *et al.*, 1998; Blanco *et al.*, 2002). Moreover, a consistent body of evidence documented antipsychotic (AP) monotherapy (and in most instances adjunctive to lithium or valproate) efficacy in acute mania, relying particularly on their fast onset of effect (Yildiz *et al.*, 2011). Certain APs have also AQ5 demonstrated utility in acute BD depression and BD relapse prevention (Cruz *et al.*, 2010; Vieta and Valentí, 2013). In some patients, APs may be preferred over mood stabilizers (MSs) because of their more favourable

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DOI: 10.1097/YIC.0000000000000283

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<zdoi;10.1097/YIC.0000000000000283>

profiles in some individuals (e.g. due to narrow therapeutic window with lithium, hepatotoxicity and teratogenic risk during pregnancy with valproate, and drug interactions with carbamazepine) and the limited placebo-controlled efficacy of MSs in bipolar depression. However, in most patients, APs are commonly associated with diverse prominent unwanted effects, including weight gain/metabolic alterations (Depp *et al.*, 2008) and akathisia (Salem *et al.*, 2017). In particular, second-generation antipsychotics (SGAs), starting with olanzapine in 2000, followed by risperidone, quetiapine, ziprasidone, and aripiprazole, received US FDA approval first for the treatment of acute mania, and later for BD maintenance (Vieta *et al.*, 2013; Yatham *et al.*, 2013; Lindström *et al.*, 2017). Moreover, the olanzapine-fluoxetine combination, quetiapine monotherapy, and lurasidone both as monotherapy and combined with lithium or valproate have obtained US FDA approval for bipolar depression treatment. These compounds are most commonly used as adjunctive to lithium or valproate, in particular for patients with BDI (Ertugrul and Meltzer, 2003; Baldessarini and Tarazi, 2005), with such combinations appearing more effective than MS monotherapy in preventing relapses and rehospitalizations during the year following a manic episode (Altamura *et al.*, 2008; Hochman *et al.*, 2016).

Decades ago, chlorpromazine obtained US FDA approval for acute mania. Moreover, even without US FDA approval for acute mania, other first-generation antipsychotics (FGAs) (haloperidol, perphenazine, fluphenazine, and thiothixene) may still have roles as effective pharmacological agents for the treatment of acute mania in clinical practice. Finally, the FGA long-acting injectable (LAI) agents perphenazine decanoate and haloperidol decanoate have demonstrated BD maintenance utility, and although having the potential for very problematic side effects in some patients, in others may be preferable to SGA LAIs.

Since the introduction of SGAs in the 1990s, FGA use gradually declined over the years, being progressively replaced even more so in America than in Europe (Depp *et al.*, 2008; Hollingworth *et al.*, 2010; Hayes *et al.*, 2011; Dehning *et al.*, 2018), in light of SGAs' apparent lower risk of inducing acute extrapyramidal side effects and dysphoria and chronic Tardive Dyskinesis. However, FGA treatment may still be a valid choice for some patients in clinical practice, at least as second-line interventions, particularly in case of specific characteristics of illness (e.g. predominant psychotic symptoms in acute mania) as well as SGA limitations (e.g. obesity, hyperlipidaemia, hyperglycaemia, availability, cost).

Indeed, a significant portion of patients with SGA inefficacy or intolerability may benefit from different and more complex therapeutic regimens, commonly based on combinations of APs and MSs, or switching strategies among these agents (Grande *et al.*, 2014).

For instance, according to the STEP-BD data, only 11% of BD patients received MS monotherapy (Ghaemi *et al.*, 2006) and approximately 30% received an AP (Simon *et al.*, 2004). The percentage of patients treated with AP polytherapy was similar in a more recent study (Degli Esposti *et al.*, 2014). It has been also estimated that about one-third of BD patients were taking lithium combined with an AP (Goldberg *et al.*, 1995), and 44% were taking both MS and AP (Depp *et al.*, 2008).

In light of the above, the aim of the present study was to examine AP (including FGA) use patterns, in a substantial sample of Northern Italian inter-episode BD patients, focussing on sociodemographic and clinical differences associated with current AP treatment, both in the whole sample and after stratifying the sample by bipolar subtype.

Methods

Subjects

The original study sample consisted of 380 Northern Italian patients currently not currently in a syndromal (hypomanic, manic, or depressive) episode with a lifetime diagnosis of bipolar I disorder (BDI) or bipolar II disorder (BDII), referred between 2011 and 2016 to the University of Milan Clinic and related community services of the Department of Mental Health, Fondazione IRCCS, Ca' Granda, Ospedale Maggiore Policlinico in Milan, Italy. The protocol was approved by the Fondazione IRCCS Ca' Granda Institutional Review Board. After explanation of study procedures, oral and written informed consent was obtained from all subjects before participation.

Assessment

Eligible patients were adults with a BDI or BDII lifetime diagnosis, formulated by psychiatrists or psychiatry residents who were trained to reliably administer the protocol interview and instruments. The diagnostic assessment was based on administration of the Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders for Axis I and Axis II disorders, Fourth Edition (American Psychiatric Association, 2000) (SCID I and SCID II, respectively) (First *et al.*, 1996; First *et al.*, 1997), by trained psychiatrists. To enhance diagnostic specificity, individuals with BD not otherwise specified were not included in the sample.

When patients had a comorbid psychiatric disorder, BD had to be the disorder primarily affecting everyday functioning, quality of life, and representing the main motivation for help-seeking.

Participants with current or lifetime diagnoses of neurological disorders, mental illnesses associated with an organic basis, mental retardation, or other disabling medical conditions were excluded.

Assessments were carried out gathering data from patients and their relatives/partners as well as from

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available clinical records and clinical observations. Sociodemographic variables included: (1) age (in years); (2) sex; (3) education; (4) current employment; (5) lifetime occupational functioning impairment; (6) cohabitation; and (7) current marital status. Assessed illness characteristics/current psychotropic medications included: (1) age at onset (in years); (2) duration of illness (in years); (3) duration of untreated illness (in years); (4) family history of psychiatric disorder (≥one first- or second-degree relative with mood disorder); (5) polarity of first episode; (6) polarity of most recent episode; (7) lifetime psychiatric hospitalization(s); (8) lifetime involuntary commitment(s) (i.e. when patients with acute and severe psychiatric symptoms, requiring urgent intervention, refused treatment and the latter could not take place in outpatient setting, thus being forced to inpatient admission, after clinical evaluation of two doctors); (9) lifetime psychosis; (10) lifetime psychosocial rehabilitation (i.e. community-based interventions used to improve social working/skills, reduce functional disability, improve quality of life, and in some instances to mitigate alcohol/substance abuse–Barbato, 2006); (11) lifetime suicide attempt(s); (12) current subthreshold mood symptoms (baseline ~~YMRS~~ > 7 but < 11, or baseline ~~HDRS~~ > 4 but < 7); (13) lifetime stressful life events; lifetime main psychiatric comorbidities (i.e. causing clinician-determined most significant distress), specifically: (14) anxiety, (15) personality, (16) alcohol/substance use, and (17) eating disorders; as well as (18) any lifetime alcohol/substance use disorder, (19) lifetime psychiatric polycomorbidity; (20) lifetime medical comorbidity; (21) current Global Assessment Functioning (GAF; Hall, 1995) to reflect patients' current level of global functioning after resolution of the most recent syndromal mood episode and excluding potential mood phase-related biases; current prescription psychotropic use, including (22) MSs (lithium and anticonvulsants–carbamazepine, valproate, and lamotrigine); (23) antidepressants (ADs: serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tryciclics, monoamine oxidase inhibitors, contemporary ADs); and (24) number of non-benzodiazepine (non-BDZ) prescription psychotropics.

All patients were grouped according to current scheduled (rather than as-needed) AP treatment and stratified by bipolar subtype (BDI and BDII). Further comparisons between BDI and BDII FGA users vs. non-users were performed.

Only subjects currently able to specifically provide the above-mentioned information were included in our analyses.

Statistical analyses

Differences between continuous parameters were assessed using independent-sample t-tests (or Mann–Whitney *U* tests, as indicated), whereas Chi-Square tests (or Fisher's Exact tests, as indicated) were used to compare categorical data. Binomial logistic regression was performed including sociodemographic and clinical variables initially found to be significantly different between AP users and non-users, with bipolar subtype as covariate.

A two-tailed significance threshold was set at $P < 0.05$, with post-hoc Bonferroni corrections for categorical variable comparisons, but no correction for multiple comparisons for continuous variable comparisons. Analyses were performed both on the whole sample and on subgroups stratified by bipolar subtype (BDI vs. BDII). Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp.; Armonk, New York, USA) on an Apple MacBook Air computer (Apple Corp., Cupertino, California, USA).

Results

Sociodemographic and clinical characteristics of current antipsychotic use

Table 1 shows the overall prevalence of bipolar patients currently taking and not taking APs along with their sociodemographic and clinical correlates, stratified by bipolar subtype. T1

From the original sample, 357 patients were selected for having information about the current AP treatment, thus being included in the statistical analyses. Of these, at time of recruitment, 292 (81.8%, 225 BDI and 67 BDII) were currently taking at least one AP, whereas 65 were not taking any AP (18.2%, 39 BDI and 26 BDII) ($P < 0.0001$).

Considering bipolar subtype, 85.2% vs. 14.8% of BDI and 72% vs. 28% of BDII ($\chi^2 = 8$, df = 1, $P = 0.005$) were taking vs. not taking APs. Patients with BDI taking APs were significantly predominant compared with those with BDII (85.2% vs. 72%, $\chi^2 = 8.0$, df = 1, $P = 0.005$).

No statistically significant difference was found in terms of sociodemographic characteristics in the overall sample of patients taking vs. not taking APs.

As for clinical characteristics, AP users vs. non-users more often had an elevated (hypo/manic rather than depressed) most recent mood episode (60.4% vs. 41.4%, $\chi^2 = 7.1$, df = 1, $P = 0.008$), and higher rates of any lifetime psychiatric hospitalization (82.5% vs. 65.0%, $\chi^2 = 9.3$, df = 1, $P = 0.002$) and psychosis (64.8% vs. 35.4%, $\chi^2 = 19.1$, df = 1, $P < 0.0001$), less frequently had anxiety disorder main comorbidity (26.0% vs. 39.7%, $\chi^2 = 4.8$, df = 1, $P = 0.029$), current AD use (29.9% vs. 52.4%, $\chi^2 = 11.7$, df = 1, $P = 0.001$), and more current overall non-BDZ psychotropic drugs (2.5 ± 0.9 vs. 1.6 ± 1.2, $F = 4.5$, $P < 0.0001$) (Fig. 1). F1

After covarying for bipolar subtype, the following variables remained statistically significant: greater lifetime psychosis rate, greater current AD use rate, and more current non-BZD psychotropic drugs (all $P < 0.02$).

In relation to the BDI subgroup, patients currently taking at least one AP were less frequently unpartnered (56.3%

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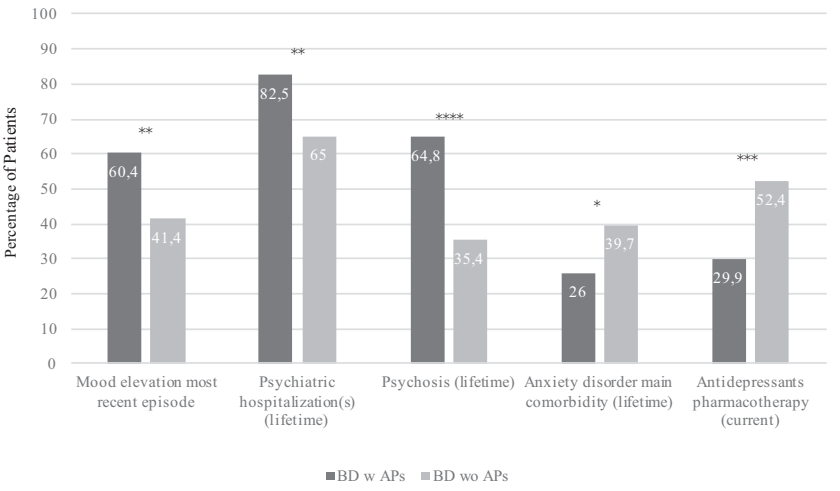
Table 1 Sociodemographic and clinical variables of bipolar patients according to the current antipsychotics treatment, in aggregate and stratified by bipolar subtype

	BDI, w APs	BDI, wo APs	BDII, w APs	BDII, wo APs	All BD, w APs	All BD, wo APs
N (%)	**225 (85.2****)	39 (14.8)	**67 (72.0****)	26 (28.0)	**292 (81.8****)	65 (18.2)
A. Age (years, mean ± SD)	47.1 ± 14.4	48.7 ± 12.3	49.2 ± 13.5	53.7 ± 16.3	47.6 ± 14.2	50.7 ± 14.2
B. Female (%)	53.8	64.1	58.2	42.3	54.8	55.4
C. Less than university degree education (%)	68.7	64.7	68.3	84.6	68.6	73.3
D. Unemployed (current, %)	39.1	47.2	22.4	32.0	35.2	41.0
E. Occupational instability (lifetime, %)	40.5	41.4	22.6	31.8	36.4	37.3
F. Living with family of origin (current, %)	27.4	23.5	16.9	15.4	24.9	20.0
G. No partner (current, %)	56.3	**75.0***	**51.5****	23.1	55.2	53.2
1. Age at onset (years, mean ± SD)	27.3 ± 10.0	28.5 ± 11.0	29.3 ± 11.7	33.1 ± 16.0	27.8 ± 10.5	30.3 ± 13.2
2. Duration of illness (years, mean ± SD)	19.7 ± 12.3	20.4 ± 10.9	19.9 ± 13.8	21.7 ± 13.3	19.8 ± 12.7	20.9 ± 11.8
3. Duration of untreated illness (years, mean ± SD)	3.4 ± 6.4	4.8 ± 7.2	7.0 ± 10.4	7.9 ± 10.7	4.2 ± 7.7	6.1 ± 8.8
4. Family history of psychiatric disorder (%)	65.5	69.2	64.2	69.2	65.2	69.2
5a. Mood elevation first episode (%)	48.1	54.8	20.0	26.1	41.3	42.6
5b. Depressive first episode (%)	51.9	45.2	80.0	73.9	58.7	57.4
6a. Mood elevation most recent episode (%)	70.8	64.7	26.6	8.3	**60.4****	41.4
6b. Depressive most recent episode (%)	29.2	35.3	73.4	91.7	39.6	**58.6****
7. Psychiatric hospitalization(s) (lifetime, %)	89.4	85.3	59.4	38.5	**82.5****	65.0
8. Involuntary commitment(s) (lifetime, %)	37.8	44.1	4.6	4.0	29.7	27.1
9. Psychosis (lifetime, %)	**79.9****	59.0	**13.6***	0.0	**64.8******	35.4
10. Psychosocial rehabilitation (lifetime, %)	15.2	11.8	7.5	7.7	13.4	10.0
11. Suicide attempt(s) (lifetime, %)	26.7	28.9	23.9	20.0	26.0	25.4
12. Subthreshold symptoms (current, %)	48.3	38.2	43.8	38.5	47.2	38.3
13. Stressful life events (lifetime, %)	57.8	55.2	63.6	66.7	59.2	60.4
Main non-BD psychiatric comorbidity (lifetime, %)						
14. Anxiety disorder	22.1	32.4	38.8	50.0	26.0	**39.7***
15. Alcohol/substance use disorder	12.2	16.2	4.5	7.7	10.4	12.7
16. Personality disorder	6.8	2.7	1.5	7.7	5.5	4.8
17. Eating disorder	3.3	2.8	4.5	0.0	3.5	1.6
18. Any alcohol/substance abuse (lifetime, %)	35.9	34.2	17.5	23.1	31.8	29.7
19. Any psychiatric policomorbidity (lifetime, %)	14.0	10.8	13.6	19.2	13.9	14.3
20. Any medical comorbidity (lifetime, %)	48.6	50.0	47.7	57.7	48.4	53.1
21. Global Assessment of Functioning (current, mean ± SD)	64.0 ± 14.5	61.9 ± 15.0	71.8 ± 11.3	73.6 ± 12.8	65.9 ± 14.2	66.6 ± 15.2
Current pharmacotherapy (%)						
22. Mood stabilizers (MSs)	68.4	64.1	53.7	69.2	65.1	66.2
23. Antidepressants (ADs)	18.1	**40.5****	68.7	69.2	29.9	**52.4*****
24. Non-BDZ prescription psychotropics (current MSs, ADs, APs, mean ± SD)	**2.5 ± 0.9******	1.3 ± 1.1	**2.7 ± 1.0*****	1.9 ± 1.3	**2.5 ± 0.9******	1.6 ± 1.2

AD, antidepressants; AP, antipsychotics; BD, bipolar disorder; BDZ, benzodiazepines; MSs, mood stabilizers; w, with; wo, without.
*$P < 0.05$, **$P \leq 0.01$, ***$P < 0.001$, ****$P < 0.0001$ with vs. without antipsychotics.

Fig. 1



Categorical variables with statistically significant differences in bipolar disorder patients with vs. without a current AP treatment. APs, antipsychotics; BD, bipolar disorder; w, with; wo, without. *$P < 0.05$, **$P \leq 0.01$, ***$P < 0.001$, **** $P < 0.0001$ with vs. without APs.

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vs. 75.0%, $\chi^2 = 4.5$, df = 1, $P = 0.034$) and had a greater rate of lifetime psychosis (79.9% vs. 59.0%, $\chi^2 = 8.1$, df = 1, $P = 0.004$). Moreover, they were currently taking more non-BDZ psychotropic drugs (2.5 ± 0.9 vs. 1.3 ± 1.1, $F = 0.9$, $P < 0.0001$) and less often taking at least one AD (18.1% vs. 40.5%, $\chi^2 = 9.5$, df = 1, $P = 0.002$).

Focussing on BDII patients, current AP use was associated with more often having single marital status (51.5% vs. 23.1%, $\chi^2 = 6.1$, df = 1, $P = 0.013$), a higher rate of lifetime psychosis (13.6% vs. 0.0%, $\chi^2 = 3.9$, df = 1, $P = 0.047$) and taking more current non-BDZ psychotropics (2.7 ± 1.0 vs. 1.9 ± 1.3, $F = 0.8$, $P = 0.001$).

Sociodemographic and clinical characteristics of current first-generation antipsychotics use

T2 Table 2 describes sociodemographic and clinical variables of BD patients in terms of current FGA use (at least one), stratified by bipolar subtype.

The overall rate of current FGAs use was 24.1% in the whole sample (86/357 patients, 80/264 BDI, and 6/93 BDII). In relation to BD subgroups, 30.3% vs. 69.7% of BDI patients and 6.5% vs. 93.5% of BDII patients ($\chi^2 = 21.4$, df = 1, $P < 0.0001$) were taking and were not taking at least one AP. BDI patients took FGAs significantly more often than did BDII patients (30.3% vs. 6.5%, $\chi^2 = 21.4$, df = 1, $P < 0.0001$).

Considering the total sample (BDI and BDII pooled), subjects currently taking at least one FGA were more frequently unpartnered (65.5% vs. 51.5%, $\chi^2 = 5.0$, df = 1, $P = 0.025$). From a clinical perspective, patients taking at least one FGA more frequently had elevated (hypo/manic rather than depressed) first (53.0% vs. 37.6%, $\chi^2 = 6.0$, df = 1, $P = 0.014$) and most recent (82.1% vs. 48.6%, $\chi^2 = 28.8$, df = 1, $P < 0.0001$) episodes, and greater rates of lifetime psychiatric hospitalization (95.0% vs. 74.6%, $\chi^2 = 15.6$, df = 1, $P < 0.0001$), involuntary commitment (50.0% vs. 22.7%, $\chi^2 = 21.4$, df = 1, $P < 0.0001$), psychosis (79.1% vs. 53.2%, $\chi^2 = 18.2$, df = 1, $P < 0.0001$), and psychosocial rehabilitation (19.5% vs. 10.7%, $\chi^2 = 4.4$, df = 1, $P = 0.037$), as well as lower mean GAF score (60.7 ± 15.3 vs. 67.7 ± 13.7, $t = 3.7$, df = 126.7, $P < 0.0001$) and AD use rate (13.1% vs. 40.4%, $\chi^2 = 21.3$, df = 1, $P < 0.0001$), but

Table 2 Sociodemographic and clinical variables of bipolar patients according to the current first-generation antipsychotics treatment, in aggregate and stratified by bipolar subtype

	BDI, w FGAs	BDI, wo FGAs	BDII, w FGAs	BDII, wo FGAs	All BD, w FGAs	All BD, wo FGAs
N (%)	80 (30.3)	**184 (69.7)******	6 (6.5)	87 (93.5)****	86 (24.1)	**271 (75.9)******
A. Age (years, mean ± SD)	47.9 ± 15.7	47.1 ± 13.4	51.8 ± 12.5	50.4 ± 14.6	48.1 ± 15.5	48.1 ± 13.9
B. Female (%)	46.3	**59.2***	50.0	54.0	46.5	57.6
C. Less than university degree education (%)	**81.3****	62.4	**33.3***	75.9	77.8	66.8
D. Unemployed (current, %)	45.5	38.0	16.7	25.6	43.4	34.0
E. Occupational instability (lifetime, %)	46.1	38.0	0.0	26.9	42.7	34.4
F. Living with family of origin (current, %)	32.9	24.1	16.7	16.5	31.7	21.6
G. No partner (current, %)	64.1	56.7	**83.3***	40.7	**65.5***	51.5
1. Age at onset (years, mean ± SD)	27.6 ± 11.2	27.5 ± 9.7	**24.5 ± 3.2****	30.8 ± 13.3	27.4 ± 10.9	28.5 ± 11.1
2. Duration of illness (years, mean ± SD)	20.3 ± 12.5	19.6 ± 12.0	27.3 ± 11.3	19.9 ± 13.7	20.8 ± 12.5	19.7 ± 12.5
3. Duration of untreated illness (years, mean ± SD)	3.2 ± 6.1	3.8 ± 6.8	9.2 ± 14.6	7.1 ± 10.2	3.6 ± 7.1	4.8 ± 8.2
4. Family history of psychiatric disorder (%)	60.0	68.7	66.7	65.5	60.5	67.7
5a. Mood elevation first episode (%)	57.1	45.0	0.0	23.2	**53.0****	37.6
5b. Depressive first episode (%)	42.9	55.0	100.0	76.8	47.0	**62.4****
6a. Mood elevation most recent episode (%)	**85.9******	62.4	33.3	20.7	**82.1******	48.6
6b. Depressive most recent episode (%)	14.1	**37.6******	66.7	79.3	17.9	**51.4******
7. Psychiatric hospitalization (lifetime, %)	**95.9***	85.8	83.3	51.2	**95.0******	74.6
8. Involuntary commitment (lifetime, %)	**53.4****	32.1	0.0	4.7	**50.0******	22.7
9. Psychosis (lifetime, %)	83.8	73.8	16.7	9.3	**79.1******	53.2
10. Psychosocial rehabilitation (lifetime, %)	18.4	13.1	**33.3****	5.7	**19.5***	10.7
11. Suicide attempts (lifetime, %)	22.5	29.0	**66.7***	19.8	25.6	26.0
12. Subthreshold symptoms (current, %)	46.1	47.2	60.0	41.2	46.9	45.1
13. Stressful life events (lifetime, %)	58.1	57.1	83.3	63.1	60.0	59.2
Main non-BD psychiatric comorbidity (lifetime, %)						
14. Anxiety disorder	19.2	25.4	66.7	40.2	22.6	30.2
15. Alcohol/substance use disorder	7.7	5.5	0.0	3.4	14.3	9.7
16. Personality disorder	15.4	11.6	0.0	5.7	7.1	4.9
17. Eating disorder	1.3	4.0	0.0	3.4	1.2	3.8
18. Any alcohol/substance abuse (lifetime, %)	39.2	34.1	40.0	17.9	39.3	28.9
19. Any psychiatric policomorbidity (lifetime, %)	15.6	12.7	**50.0***	12.8	18.1	12.7
20. Any medical comorbidity (lifetime, %)	48.8	48.9	50.0	50.6	48.8	49.4
21. Global Assessment of Functioning (current, mean ± SD)	**60.1 ± 15.6****	65.3 ± 13.9	67.5 ± 10.4	72.7 ± 11.8	60.7 ± 15.3	**67.7 ± 13.7******
Current pharmacotherapy (%)						
22. Mood stabilizers	68.8	67.4	66.7	57.5	68.6	64.2
23. ADs	10.3	**26.1****	50.0	70.1	13.1	**40.4******
24. Non-BDZ prescription psychotropics (current MSs, ADs, APs, mean ± SD)	**2.7 ± 0.8******	2.1 ± 1.1	**3.5 ± 0.8***	2.4 ± 1.1	**2.8 ± 0.9******	2.2 ± 1.1

ADs, antidepressants; APs, antipsychotics; BD, bipolar disorder; BDZ, benzodiazepines; FGAs , first generation antipsychotics; w, with; wo, without.
*$P < 0.05$, **$P \leq 0.01$, ***$P < 0.001$, ****$P < 0.0001$ with vs. without FGAs.

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more current non-BDZ psychotropic drugs (2.8 ± 0.9 vs. 2.2 ± 1.1, $t = -5.0$, df = 180.3, $P < 0.0001$) (Fig. 2).

With regard to the BDI subset, current FGA users vs. non-users more frequently had lower education status (81.3% vs. 62.4%, $\chi^2 = 8.6$, df = 1, $P = 0.003$). As for illness characteristics, BDI users vs. non-users more frequently had an elevated (hypo/manic rather than depressed) most recent episode (85.9% vs. 62.4%, $\chi^2 = 13.9$, df = 1, $P < 0.0001$), and higher lifetime psychiatric hospitalization (95.9% vs. 85.8%, $\chi^2 = 5.4$, df = 1, $P = 0.20$) and involuntary commitment (53.4% vs. 32.1%, $\chi^2 = 9.7$, df = 1, $P = 0.002$) rates, lower mean GAF scores (60.1 ± 15.6 vs. 65.3 ± 13.9, $t = 2.6$, df = 248, $P = 0.009$) and a lower AD use rate (10.3% vs. 26.1%, $\chi^2 = 8.2$, df = 1, $P = 0.004$), but more current non-BDZ psychotropic drugs (2.7 ± 0.8 vs. 2.1 ± 1.1, $t = -4.6$, df = 261, $P < 0.0001$).

Referring to individuals with BDII, those currently taking vs. not taking at least one FGA more often had lower education status (33.3% vs. 75.9%, $\chi^2 = 5.2$, df = 1, $P = 0.023$) and were more frequently unpartnered (83.3% vs. 40.7%, $\chi^2 = 4.2$, df = 1, $P = 0.042$). Individuals with BDII taking vs. not taking at least one FGA had an earlier age at onset (24.5 ± 3.2 vs. 30.8 ± 13.3, $t = 3.3$, df = 23.2, $P = 0.003$), and higher rates of lifetime psychosocial rehabilitation (33.3% vs. 5.7%, $\chi^2 = 6.1$, df = 1, $P = 0.013$), suicide attempt (66.7% vs. 19.8%, $\chi^2 = 7.0$, df = 1, $P = 0.008$), psychiatric polycomorbidity (50.0% vs. 12.8%, $\chi^2 = 6.0$, df = 1, $P = 0.014$), and were currently taking more non-BDZ psychotropic drugs (3.5 ± 0.8 vs. 2.4 ± 1.1, $t = -2.3$, df = 91, $P = 0.023$).

Supplementary analyses on subtypes of AP used revealed that 24.1% vs. 75.9% of the whole sample (30.3% of BDI, 6.5% of BDII) ($P < 0.0001$) were currently taking exclusively FGAs, 74.0% vs. 26% exclusively SGAs (75.4% of BDI, 69.9% of BDII) ($P < 0.0001$), whereas 15.7% vs. 84.3% (19.7% of BDI, 4.3% of BDII) ($\chi^2 = 12.3$, df = 1, $P < 0.0001$) were taking FGAs combined with SGAs.

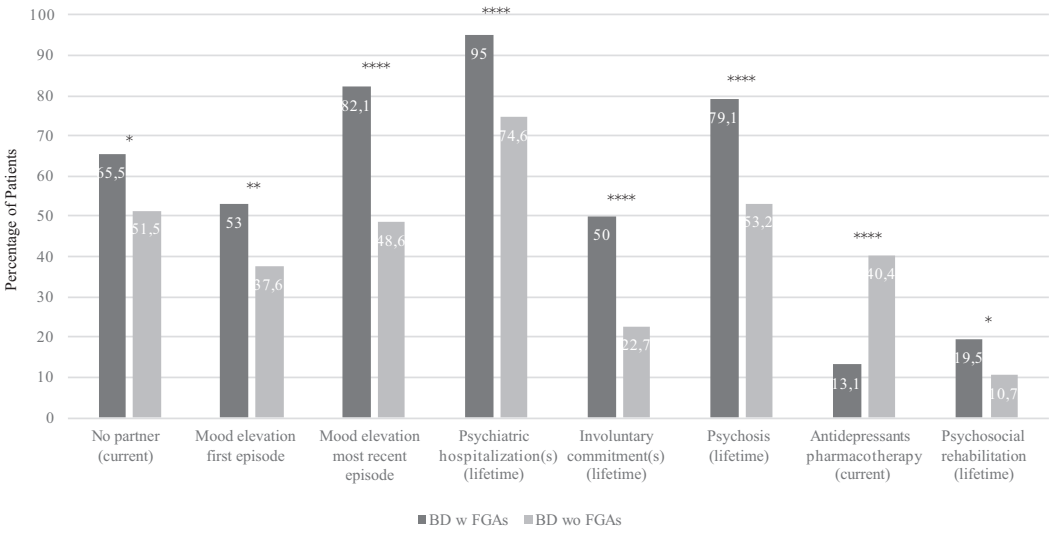
In addition, the two most common FGAs administered in the whole sample were zuclopenthixol and haloperidol, followed by levomepromazine, promazine, chlorpromazine, and pimozide. With respect to SGAs, the most commonly prescribed ones were quetiapine, olanzapine, aripiprazole, followed by asenapine and paliperidone.

Discussion

In the present study, we sought to assess potential differences between BD patients with vs. without current AP use, considering not only SGAs but also FGAs. We found that, in the whole sample and in the BDI and BDII diagnostic subgroups, patients taking vs. not taking APs at the time of ~~enrolment~~ were numerically predominant. The nature of our sample, mainly consisting of BDI patients–all of whom were inter-episode (though some of them may have been still recovering)–may partially explain the high rate of AP use (i.e. at least some patients were in the continuation rather than the maintenance treatment phase).

Our AP utilization rate seemed slightly higher although in line with the rising trend reported in most recent population-based studies, analysing longitudinal patterns

Fig. 2



Categorical variables with statistically significant differences in bipolar disorder patients with vs. without a current FGA treatment. FGAs, first-generation antipsychotics; BD, bipolar disorder; w, with; wo, without. *$P < 0.05$, **$P \leq 0.01$, ***$P < 0.001$, ****$P < 0.0001$ with vs. without APs.

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of prescription psychopharmacological treatment in BD patients (Chang *et al.*, 2016; Kessing *et al.*, 2016). Indeed, according to Kessing *et al.* (2016), APs went from being the third most prescribed class in 2000 to the most prescribed class in 2011 (taken by 61.5% of patients currently in remission), with a cumulative incidence of 60.8% and an increased 1-year prescription risk. Chang *et al.* (2016) found AP utilization rate rose from 50.7% in 2001 to 70.4% in 2010, with SGA use rates increasing more than fivefold (from 9.7% to 53.3%), and FGA use rates decreasing less dramatically (from 48.4 to 37.6%). In addition, Vieta *et al.* (2013) reported APs to be the most prescribed drug class, with a comparable prevalence, largely independent of BD illness phase, except for depressive episodes.

Previous studies reported heterogeneous AP use rates in BD patients, mostly depending on BD illness phase and therapeutic setting. Frangou *et al.* (2002) reported a 36.5% exposure rate among 63 BDI patients at last assessment, although 85.7% had previously received APs. In a pre-SGA era review by Tohen and Zarate (1998), AP exposure rates ranged between 55% and 100%, with a 68% pooled estimate. Similarly, Sernyak and Rosenheck (2004) reported 67% of stable BD outpatients were taking APs, whereas Keck *et al.* (1996) found that 68% of BD patients took APs 6 months after hospital discharge. More recently, Paterniti and Bisserbe (2013) reported that 45.1% of BD patients referred to a tertiary care service were taking APs with SGAs predominant, as high as 57.1% during euthymia and 61.1% during depression among BDI patients.

Our overall AP use was more prevalent among BDI vs. BDII subjects, being in line with previous results from our group and consistent with the observed BDI clinical profile, characterized by a higher rate of lifetime hospitalizations and involuntary commitments, and more frequent elevated (hypo/manic rather than depressed) last episode polarity vs. BDII patients (Dell'Osso *et al.*, 2017). As expected, such significant differences, along with a higher lifetime psychosis rate, emerged in the whole sample of AP users vs. non-users. This is consistent with previous results from literature underlining associations between AP use, history of lifetime psychosis, and manic presentations (Licht *et al.*, 1994; Keck *et al.*, 1996; Verdoux *et al.*, 1996; Soares *et al.*, 1999; Levine *et al.*, 2001; Dell'Osso *et al.*, 2017), as well as with a higher number of manic episodes and a history of mood-incongruent psychotic features (Frangou *et al.*, 2002).

In relation to sociodemographic features, marital status significantly differed in AP users vs. non-users across diagnostic subgroups, but not in the whole sample. For instance, BDI AP users were less frequently unpartnered, whereas individuals with BDII taking vs. not taking APs were more often single. In such regard, we may speculate that APs may more positively influence relationship-toxic manic- rather than depressive-related challenges among partners.

Current AP users vs. non-users, either BDI or BDII, also were currently taking more non-BDZ psychotropic drugs. For instance, if, on one hand, the availability of a wide range of therapeutic strategies for BD treatment may yield better clinical outcomes, on the other hand, it may increase the risk of a psychotropic polypharmacy, found to be greater in BD than in other common psychiatric diagnoses (Mojtabai and Olfson, 2010). This may warrant clinical attention because of concerns about its safety, tolerability, and cost-effectiveness (Alda and Yatham, 2009).

BDI, but not BDII current AP users vs. non-users, less frequently had current AD use. As our sample consisted of recovered and recovering patients, the use of ADs may be related to the potential presence of residual symptoms from the last episode. However, although subthreshold symptoms appeared marginally greater in current AP users, AD use was lower as well. This may be due to the polarity of last episode (more frequently manic vs. depressive) and relative potential residual symptoms of the same polarity, likely better controlled with APs. Again, the nature of the sample, with a predominant BDI diagnosis, may partially explain this finding. From a wider perspective, it could be also related to a more cautious AD administration in bipolar patients–recommended during depressive phases only and combined with antimanic agents (Grunze *et al.*, 2010; Pacchiarotti *et al.*, 2013; Yatham *et al.*, 2013; National Institute for Health and Care Excellence, 2014) due to the risks of switching to mood elevation and rapid cycling (which were lower in BDII vs. BDI patients, Altshuler *et al.*, 2006)–in favour of the AD properties of some APs (Cruz *et al.*, 2010), or the tendency to retain ADs and lithium longer than other psychotropics (i.e. anticonvulsants, APs, and sedatives) (Baldessarini *et al.*, 2007). Indeed, there is only limited evidence of AD efficacy and safety in the treatment of bipolar depression (Ghaemi *et al.*, 2008; Sidor and MacQueen, 2011). Nevertheless, ADs remain the most commonly prescribed medications in BD in the United States, both initially and over the long-term (Baldessarini *et al.*, 2008). In particular, clinicians tend to use ADs in case of residual depressive symptoms, which represent important contributors to substance abuse, functional impairment, and mortality due to high suicide rates in earlier years (Frye *et al.*, 2006).

In relation to MS treatment, around two-thirds of patients taking APs were doing so along with MSs. However, BD patients not currently taking APs had MS use rates not significantly different from AP users.

Furthermore, in the pooled sample of all (BDI plus BDII) patients, those taking vs. not taking APs more frequently had an elevated most recent episode and a higher rate of lifetime psychiatric hospitalization. With respect to these results, a mood-elevated most recent episode may have yielded ongoing AP augmentation of MSs. However, the above observations were not statistically significant

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among the BDI and BDII diagnostic subgroups, possibly due to lower statistical power when considering these subgroups separately.

In the present study, we decided to assess not only SGA but also FGA use. In fact, to date, most of the contemporary literature on BD maintenance treatment is focussed on SGAs. Although since their introduction, SGAs have been increasingly replacing FGAs in BD treatment (Pillarella *et al*., 2012), according to a recent report, FGA prescriptions merely had a small non-significant decrease in treatment of manic/mixed phases, but a significant reduction in depressive episodes (this could be related to increasing evidence of association between FGA use and depression), suggesting that in certain contexts FGAs are still appreciated by clinicians (Dehning *et al*., 2018).

In our sample, FGAs were administered to roughly one-fourth of the total sample, one-third of BDI patients, and only 6.5% of BDII patients. This use appears in line with more AP use in BDI vs. BDII patients, in both the present article and in a previous report by our group (Dell'Osso *et al*., 2017).

In relation to sociodemographic variables, FGA users vs. non-users were found to be more frequently unpartnered. The same finding was replicated in the BDII subgroup, though it did not reach statistical significance among BDI patients. Moreover, education level was lower in BDI but higher in BDII subjects currently taking FGAs.

With respect to clinical correlates, BD patients currently taking FGAs more frequently had elevated first and most recent mood episodes, higher lifetime rates of psychiatric hospitalization, involuntary commitment, psychosis, and psychosocial rehabilitation, and lower current mean GAF score. Some of these results, including higher rates of mood elevation for most recent episode, lifetime hospitalization, and lifetime involuntary commitment, were also found in BDI FGA users vs. non-users. Conversely, BDII patients currently taking vs. not taking FGAs had an earlier age at onset, and higher rates of lifetime suicide attempt, psychosocial rehabilitation, and psychiatric poly-comorbidity. However, limited statistical power due to the small size of our BDII sample did not permit drawing conclusions.

As for current pharmacological treatment, the overall, BDI and BDII groups taking vs. not taking APs were more likely to take more non-BDZ psychotropic drugs, but less frequently ADs, except for BDII group (as the latter comparison did not reach the statistical significance).

Strengths of our study include assessing AP use, rather than AP prescribing patterns, within a substantial well-characterized bipolar sample recruited from different psychiatric services. This may reliably reflect psychotropic rates in psychiatric clinical practice, by at least partially overcoming potential issues related to patient adherence. Furthermore, this design allowed investigating correlates of both SGA and FGA utilization by BD subtype.

The above-mentioned findings should be interpreted within the context of some noteworthy limitations, including the naturalistic (non-randomized) nature of our sample, which precluded causality assessment, as AP use could drive clinical correlates or vice-versa. The generalizability of our results may be limited by the inclusion in our sample of mainly lifetime hospitalized Northern Italian BD patients, thus not representative of all BD patients, as well as of inter-episode patients (recovered or recovering), thus leading to a potential selection bias. Furthermore, our assessments did not include doses of prescribed medications or distinctions between initial mono- or adjunctive AP treatment, length of AP treatment, potential reasons for discontinuation or augmentation, changes in AP medications, and adherence to treatment. In particular, inter-episode treatment may not reflect long-term therapy, at least in those patients with short duration of illness, being it closely related to the polarity of the index episode that led to hospital admission, rather than to the predominant polarity of illness. Moreover, it is worth considering that manic rather than depressive phases may more frequently result in hospital admissions, either voluntary or involuntary, thus introducing a potential bias. Finally, statistical power was less robust in our FGA and BDII analyses, due to limited subsample size.

It is also worth noting that, although patients could be currently taking combination therapy, we grouped patients in terms of taking vs. not taking medication from a single (i.e. AP) medication class.

Nevertheless, we contend that our present findings ought to encourage future investigation of SGAs vs. FGAs in bipolar subtypes across different illness phases, as this may help in assessing the appropriateness of psychotropic use.

Acknowledgements

The present study was conducted according to the principles expressed in the Declaration of Helsinki and partially supported by a research grant (Scientific Productivity Fund), annually provided by the Fondazione IRCCS Ca' Granda of Milan.

Conflicts of interest

There are no conflicts of interest.

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