Original Paper

Side effects associated with psychotropic medications in patients with bipolar disorder: evidence from two independent samples

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Abstract

Available evidence concerning the side effects experienced by bipolar disorder (BD) patients under naturalistic conditions has been poorly investigated. The aim of this study was therefore to investigate side effects related to major psychotropic drugs in two independent samples of BD patients naturalistically treated with mood stabilizers, antidepressants, antipsychotics and/or anxiolytics. Overall, 3654 patients from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample and 282 patients from the Clinical Outcome and Psycho-Education for Bipolar Disorder (COPE-BD) sample were included. The primary outcome measure was the influence of each class of psychotropic drugs under investigation on the emergence of any side effect, as measured with the monitoring form in the STEP-BD study and the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale in the COPE-BD study. Secondary outcome measures included the effects of such drugs on psychic, neurologic, autonomic and other side effects. Mood stabilizers and antipsychotics were associated with high rates of side effects in both samples. Furthermore, antipsychotics were specifically associated with psychic side effects, whereas mood stabilizers were specifically associated with neurologic side effects. Our results largely confirm in a naturalistic setting results previously observed in randomized controlled trials focusing on BD patients.

Keywords

Side effects, bipolar disorder, mood stabilizers, antidepressants, antipsychotics, anxiolytics

Introduction

Bipolar disorder (BD) is a disabling, often chronic, mental disorder with an estimated likelihood of occurring over the life span as high as 1-4% (Hirschfeld et al., 2003; Merikangas et al., 2007; Ten Have et al., 2002). In spite of the lower prevalence of such disorder in comparison with other mental disorders such as major depression (Kessler et al., 2003), the consequences of BD may be far more dramatic. Just to mention some examples, BD patients have a higher likelihood of attempting and completing suicide, of perceiving a poorer quality of life and of experiencing a higher number of illness-related limitations as compared with patients suffering from other mental disorders (Baldessarini et al., 2006; Ten Have et al., 2002). As a consequence, effective and well tolerated treatments for BD patients are an issue of paramount importance for clinicians involved with such patients and for the health-care system.

Several treatment options are currently available for the treatment of BD. According to current guidelines, the treatment of manic/hypomanic and mixed episodes should generally start with a mood stabilizer, such as lithium or valproate, or with an atypical antipsychotic, such as aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone as monotherapy (Connolly and Thase, 2011; Fountoulakis et al., 2012; Nivoli et al., 2012). Combination therapy, including lithium or valproate and an atypical antipsychotic, should usually be considered as a second line choice (Connolly and Thase, 2011; Fountoulakis et al., 2012; Nivoli et al., 2012). Moreover, the use of adjunctive benzodiazepines is recommended in cases of agitation, sleep complaints and behavioral disturbances (Connolly and Thase, 2011; Nivoli et al., 2012).

On the other hand, the combination with best data in acute bipolar depression is lithium+lamotrigine (Fountoulakis et al., 2012). Further options include quetiapine mono-therapy or alternatively a fluoxetine/olanzapine combination (Connolly and Thase, 2011; Nivoli et al., 2011). Finally, taking into account the risk of antidepressant-induced mania and rapid cycling (Nivoli et al., 2011; Sachs et al., 2007), antidepressants should be used only in combination with mood stabilizing agents (Fountoulakis et al., 2012).

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As one can observe from this brief overview, the treatment of BD usually involves the use of pharmacological compounds belonging to different classes of psychotropic drugs, including mood stabilizers, antipsychotics, antidepressants and anxiolytics. This, in turn, raises the critical issue of the emergence of unwanted side effects related to this large variety of drugs, employed either alone or in combination with one another, and the consequent possibility of low adherence to prescribed medications (Velligan et al., 2009). Of note, although the burden of side effects of all these drugs has been extensively studied in several rigorous randomized controlled trials (RCTs) usually focusing on selected samples of BD patients without co-morbid psychiatric disorders (Berk and Berk, 2003; Papakostas, 2010; Rummel-Kluge et al., 2010; Uzun et al., 2010), available evidence concerning the side effects of such drugs under naturalistic conditions is far less clear. This is a particularly important issue, because current evidence suggests that significant discrepancies might exist between the characteristics of patients and side effects reported in RCTs as compared with those observed in 'real world' clinical practice (e.g. Meltzer and Bobo, 2006; Zetin et al., 2006). In addition, it is unclear whether the side effect burden of BD patients naturalistically treated with different drugs or combinations of drugs could vary as function of the specific characteristics of the sample under investigation in each study, or whether this burden can be generalized across different samples (Berk and Berk, 2003; Brooks et al., 2011; Miller et al., 2001; Velligan et al., 2009).

Accordingly, the aims of this study were (a) to investigate the side effects related to psychotropic drugs in two large independent samples of BD patients (the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample and the Clinical Outcome and Psycho-Education for Bipolar Disorder (COPE-BD) sample) naturalistically treated with mood stabilizers, antidepressants, antipsychotics and/or anxiolytics, and (b) to investigate which side effects can be observed in both samples, regardless of possible differences in terms of socio-demographic and clinical variables.

Methods

Samples

STEP-BD sample: Clinical data were retrieved from the National Institute of Mental Health (NIMH) funded STEP-BD project (Sachs et al., 2003). The STEP-BD was a long-term outpatient study designed to investigate which treatments, or combinations of treatments, are most effective for treating episodes of depression and mania and for preventing recurrent episodes in BD. It enrolled more than 4000 patients, being one of the largest studies ever performed worldwide for this disease. The study had very broad inclusion criteria. Indeed, both bipolar patients and patients with the bipolar subtype of schizoaffective disorder in every phase of their disease were enrolled. A detailed description of inclusion/exclusion criteria can be found elsewhere (Sachs et al., 2003).

Briefly, the STEP-BD used a hybrid design to collect longitudinal data as patients made transitions between naturalistic studies and RCTs. Eligible subjects with an age ≥15 years were entered into a study registry. All patients received a systematic assessment battery at study entry and were treated by a psychiatrist (trained to deliver care and measure outcomes in BD patients) using a series of model practice procedures consistent with expert recommendations (Sachs et al., 2003). At each follow-up visit, the treating psychiatrist completed a standardized assessment and assigned an operationalized clinical status based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (DSM-IV) criteria (American Psychiatric Association, 1994). The follow-up visits were not time scheduled but the timing of visits was left to the psychiatrists' and patients' decision, as the naturalistic setting of the first branch of the study required. For the purposes of the present study we focused on the naturalistic part of the study and we included only BD patients for which reports of side effects were available.

COPE-BD sample: Patients were recruited within the 'Psy Pluriel' center, Centre Européen de Psychologie Médicale and the Department of Psychiatry of Erasme Hospital in Brussels. A detailed description of the sample has been reported elsewhere (Souery et al., 2011, 2012). In sum, in this project the assessment of mood disorder patients was completed using a software program, 'COPE-Bipolar.COM' (Clinical Outcome Measures for Bipolar Disorder), consisting of a structured examination tool and immediate data capture. It is composed of 10 'modules', each of which is dedicated to essential elements of mood disorders, such as socio-demographic characteristics, psychiatric antecedents, diagnosis, treatment, and quality of life and functioning. Lifetime and current diagnosis, course of illness and comorbidities were assessed by trained psychiatrists on the basis of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients were included if they met DSM-IV criteria for a diagnosis of mood disorders (BD and major depression). In this paper we only focused on BD patients for which side effects were available.

Outcome measures

The primary outcome measure of this study was the influence of taking vs not taking mood stabilizers, antidepressants, antipsychotics and anxiolytics, as well as of the total amount of drugs within each of these classes (none, 1, 2 or >2 drugs for each class), on experiencing at least one clinically relevant side effect (see below). Secondary outcomes included the influence of taking vs not taking mood stabilizers, antidepressants, antipsychotics and anxiolytics, as well as of the total amount of drugs within each of these classes, on (a) psychic, (b) neurologic, (c) autonomic and (d) other side effects separately considered. Both primary and secondary outcome measures were independently investigated in the two samples, so as to investigate which side effects can be observed regardless of possible differences in terms of socio-demographic and clinical variables, as well as study design and measurement instruments employed to investigate side effects within each sample, as well as in the combined sample (STEP-BD + COPE-BD patients joined together).

Furthermore, pertaining to the secondary outcomes, in case of associations in both samples, we performed further analyses focusing on the influence of specific classes of drugs (e.g., antipsychotics) on each single side effect belonging to a group of side effects (e.g., psychic side effects) with evidence of association with that class of drugs. Following the identification of which side effect (or effects) drove the association between a class of drugs and a class of side effects, as a third step of analyses we investigated the associations between specific drugs or drug combinations and the specific side effects observed in the second set of analyses.

Assessment of side effects

In the STEP-BD study, the presence and severity of side effects were rated on a Clinical Monitoring Form (CMF) for a series of side effects (Sachs et al., 2002), including constipation, diarrhea, dry mouth, extrapyramidal signs, tremors, headache, sedation, memory reduction, weight gain and sexual dysfunction. Side effects were rated on a five-point Likert scale ranging from 0 (no side effect) to 4 (extremely severe side effect). As the STEP-BD had a longitudinal course, in order to allow for a higher comparability with the COPE-BD study (see below) and to maximize the sensitivity to the detection of side effects in this sample, we considered the visit in which subjects showed the largest number of side effects. For subjects who did not show any side effect over the study period, we chose the visit that was closer to the mean time of the overall follow-up period (day 214).

In the COPE-BD study, the presence and severity of side effects were rated using the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987). The UKU assesses a total of 48 symptoms arranged into four groups: psychic, neurologic, autonomic and other side effects. Each symptom is scored from 0 (no side effect) to 3 (side effect that markedly interferes with patient's performance). As this study was cross-sectional, side effects were recorded at a single time point. In order to match the presence of side effects in the STEP-BD and in the COPE-BD samples as much as possible, we dichotomized the presence of side effects in both studies. Furthermore, in order to match the structure of the UKU employed in the COPE-BD study, we categorized the side effects available for the STEP-BD sample into four different classes including psychic, neurologic, autonomic and other side effects (see below).

First of all, in accordance with a number of previous studies employing the UKU scale as a measure of side effects related to psychotropic drugs (e.g. De Leon et al., 2005; Demyttenaere et al., 2005), we dichotomized patients experiencing no or mild side effects that did not interfere with patient's function as not having side effects, and patients experiencing moderate to severe side effects that had a significant impact on patient's functioning as having side effects. Similarly, in the STEP-BD sample we dichotomized patients experiencing none or mild side effects that did not interfere with patient's functioning (score 0 or 1) as not having side effects and patients experiencing moderate to severe side effects (score from 2–4) as having side effects.

Secondly, as an example, a patient was rated as experiencing psychic side effects if he/she reported at least one psychic side effect. Moreover, a patient was rated as experiencing at least one side effect if he/she experienced at least one psychic, neurologic, autonomic or other side effects. Finally, as reported above, the 10 side effects that were investigated in the STEP-BD study were categorized into four distinct classes of side effects in order to match as much as possible the structure of the UKU scale. In particular, sedation and memory reduction were rated as psychic side effects; tremors and extrapyramidal effects were rated as neurologic side effects; dry mouth, constipation and diarrhea were rated as autonomic side effects and headache, weight gain and sexual dysfunction were rated as other side effects.

Statistical analyses

Descriptive statistics are presented as percentages for discrete variables and as mean±standard deviation (SD) for continuous variables. A χ^2 statistic was used to compare the distribution of discrete characteristics between patients experiencing at least one side effect and those experiencing no side effects as well as the general characteristics of the two samples. Comparisons of continuous characteristics by the presence or absence of side effects were completed using the Student *t*-test. Analysis of covariance and binomial regression models were used to determine the independent association of the presence vs absence of side effects related to each class of drugs independently considered, after adjusting for potential confounders (i.e. socio-demographic and clinical variables that were associated with the outcome of interest and for which there is evidence of a possible influence on the observed outcome including, as an example, the association between currently depressive mood and a higher likelihood of perceiving side effects, e.g. Watson, 1988). In addition, in case of associations between specific classes of drugs (e.g. antipsychotics) and specific side effects (e.g. sedation) we calculated the number needed to harm (NNH) as well the number needed to treat (NNT) (http://www.nntonline.net).

Statistical significance was conservatively set at a *p*-value $\leq$0.002, corresponding to the Bonferroni correction for multiple testing (nearly 20 analyses on the main outcome measure). With these parameters we had a sufficient power (0.80) to detect a small effect size of 0.07 corresponding, for instance, to the possibility of detecting an odds ratio (OR) of 1.32 between patients experiencing and those not experiencing side effects in the STEP-BD study and a small–medium effect size of 0.23 corresponding, for instance, to the possibility of detecting an OR of 2.4 between patients experiencing and those not experiencing side effects in the COPE-BD study (Cohen, 1988). In other words, the large sample-size of the COPE-BD and the very large sample-size of the STEP-BD studies allowed us to detect very small differences that could otherwise be missed in smaller samples.

Results

Socio-demographic and clinical characteristics of the samples

Socio-demographic and clinical characteristics of the samples are shown in Table 1 and Supplementary Material, Table 1. Overall, 3654 patients from the STEP-BD sample and 282 patients from the COPE-BD sample have been included. Differences were observed between the two samples in terms of several socio-demographic and clinical variables. However, the two groups did not differ in terms of gender, comorbid obsessive compulsive disorder, alcohol and substance abuse, use of antipsychotics, psychic and autonomic side effects (see Supplementary Material, Table 1 for further details).

Primary outcome measure: effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on total side effects in the STEP-BD and in the COPE-BD sample

In the STEB-BD sample, associations were observed between the use and the number of mood stabilizers, antipsychotics, antidepressants and anxiolytics and total side effects. In particular, patients taking as compared with those not taking such drugs, as

Table 1. Socio-demographic and clinical variables in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample, in the Clinical Outcome and Psycho-Education for Bipolar Disorder (COPE-BD) sample and in the global sample (STEP-BD + COPE-BD joined together) stratified according to the presence or absence of at least one side effect. OCD: obsessive compulsive disorder; SD: standard deviation. [a]Significant associations. [b]Patients are classified as taking two or more drugs if they are taking at least two among the following classes of drugs: 'mood stabilizers' or 'antidepressants' or 'antipsychotics'.

Socio-demographic and clinical variables	Patients with at least one side effect in the STEP-BD sample (*n*=2617)	Patients with no side effects in the STEP-BD sample (*n*=1037)	χ^2 or *F*	*p*-values	Patients with at least one side effect in the COPE-BD sample (*n*=157)	Patients with no side effects in the COPE-BD sample (*n*=125)	χ^2 or *F*	*p* -values	Patients with at least one side effect in the global sample (*n*=2774)	Patients with no side effects in the global sample (*n*=1162)	χ^2 or *F*	*p* -values
Gender			15.41	0.00009[a]			0.0004	0.98			13.43	0.0002[a]
Males	991(38%)	453(44%)			63(40%)	50(40%)			1054(38%)	503(43%)		
Females	1500(57%)	508(49%)			94(60%)	75(60%)			1594(57%)	583(50%)		
Missing	126(5%)	76(7%)							126(5%)	76(7%)		
Age	40.29±12.60	39.13±13.53	5.58	0.02	51.04±13.95	45.84±13.13	10.17	0.002[a]	40.92±12.93	39.91±13.65	4.68	0.03
Marital status			1.92	0.16			4.26	0.04			2.12	0.14
Married/living with a partner	956(37%)	338(33%)			91(58%)	57(46%)			1047(38%)	395(34%)		
Other	1548(59%)	611(59%)			66(42%)	68(54%)			1614(58%)	679(58%)		
Missing	113(4%)	88(8%)							113(4%)	88(8%)		
Ethnicity			0.90	0.34			1.34	0.24			0.07	0.78
Caucasian	2162(83%)	822(79%)			149(95%)	122(98%)			2311(83%)	944(81%)		
Other	327(12%)	138(13%)			8(5%)	3(2%)			335(12%)	141(12%)		
Missing	128(5%)	77(8%)							128(5%)	77(7%)		
Education			3.51	0.17			2.59	0.27			2.60	0.27
Primary education	16(1%)	11(1%)			10(6%)	3(2%)			26(1%)	14(1%)		
Secondary education	1361(52%)	529(51%)			103(66%)	82(66%)			1464(53%)	611(53%)		
University	1121(43%)	402(39%)			43(27%)	38(30%)			1164(42%)	440(38%)		
Missing	119(4%)	95(9%)			1(1%)	2(2%)			120(4%)	(38%)		
Professional status			10.60	0.005			6.59	0.04			11.11	0.004
Employed	1108(42%)	457(44%)			87(55%)	52(42%)			1195(43%)	509(44%)		
Unemployed	613(24%)	244(23%)			14(9%)	22(18%)			627(23%)	266(23%)		
Other	767(29%)	236(23%)			28(18%)	20(16%)			795(29%)	256(22%)		
Missing	129(5%)	100(10%)			28(18%)	31(25%)			157(5%)	131(11%)		
Age of onset			0.23	0.88			1.62	0.44			0.45	0.80
<30 years	2242(86%)	880(85%)			111(71%)	94(75%)			2353(85%)	974(84%)		
30–45 years	260(10%)	96(9%)			36(23%)	22(18%)			296(11%)	118(10%)		
>45 years	51(2%)	20(2%)			6(4%)	7(6%)			57(2%)	27(2%)		
Missing	64(2%)	41(4%)			4(2%)	2(2%)			68(2%)	43(4%)		
Current depressive episode			35.23	<0.000001[a]			1.46	0.22			11.80	0.00002[a]
Yes	692(26%)	178(17%)			74(47%)	68(54%)			766(28%)	246(21%)		
No	1925(74%)	859(83%)			83(53%)	57(46%)			2008(73%)	916(79%)		
Current hypomanic episode			2.87	0.10			0.28	0.59			4.68	0.03
Yes	56(2%)	32(3%)			10(6%)	10(8%)			66(2%)	42(4%)		
No	2561(98%)	1005(97%)			147(94%)	115(92%)			2708(98%)	1120(96%)		
Current manic episode			5.49	0.02			0.003	0.95			1.18	0.28
Yes	55(2%)	10(1%)			16(10%)	13(10%)			71(3%)	23(2%)		
No	2562(98%)	1027(99%)			141(90%)	112(90%)			2703(97%)	1139(98%)		

Table 1. (Continued)

Socio-demographic and clinical variables	Patients with at least one side effect in the STEP-BD sample (*n*=2617)	Patients with no side effects in the STEP-BD sample (*n*=1037)	χ^2 or *F*	*p*-values	Patients with at least one side effect in the COPE-BD sample (*n*=157)	Patients with no side effects in the COPE-BD sample (*n*=125)	χ^2 or *F*	*p* -values	Patients with at least one side effect in the global sample (*n*=2774)	Patients with no side effects in the global sample (*n*=1162)	χ^2 or *F*	*p* -values
Suicidal risk			19.97	0.0001[a]			1.74	0.62			5.46	0.02
None/low	2413(92%)	997(96%)			99(63%)	81(65%)			2512(91%)	1078(93%)		
Moderate/high	204(8%)	40(4%)			58(37%)	44(35%)			262(9%)	84(7%)		
Psychotic features			13.63	0.0002[a]			0.09	0.76			8.17	0.004
Yes	118(4%)	20(2%)			17(11%)	13(10%)			135(5%)	33(3%)		
No	2482(95%)	1011(97%)			136(87%)	107(86%)			2618(94%)	1118(96%)		
Missing	17(1%)	6(1%)			4(2%)	5(4%)			21(1%)	11(1%)		
Comorbid anxiety disorders			9.28	0.003			0.46	0.49			8.50	0.003
Yes	979(38%)	309(30%)			78(50%)	57(46%)			1057(38%)	366(31%)		
No	1473(56%)	603(58%)			79(50%)	68(54%)			1552(56%)	671(58%)		
Missing	165(6%)	125(12%)							165(6%)	125(11%)		
Comorbid OCD			3.20	0.07			0.22	0.63			2.99	0.08
Yes	192(7%)	55(5%)			15(10%)	10(8%)			207(8%)	65(6%)		
No	2254(86%)	856(83%)			137(87%)	112(90%)			2391(86%)	968(83%)		
Missing	171(7%)	126(12%)			5(3%)	3(2%)			176(6%)	129(11%)		
Alcohol dependence			0.96	0.32			0.26	0.60			0.78	0.37
Yes	202(8%)	66(6%)			9(6%)	9(7%)			211(8%)	75(6%)		
No	2241(86%)	846(82%)			148(95%)	115(92%)			2389(86%)	961(83%)		
Missing	174(6%)	125(12%)			0(0%)	1(1%)			174(6%)	126(11%)		
Drug dependence			1.69	0.19			0.25	0.61			2.02	0.15
Yes	120(4%)	55(5%)			8(5%)	8(6%)			128(5%)	63(5%)		
No	2319(89%)	855(83%)			149(95%)	115(92%)			2468(89%)	970(84%)		
Missing	178(7%)	127(12%)			0(0%)	2(2%)			178(6%)	129(11%)		
Physical comorbidities			12.50	0.0004[a]			2.63	0.10			17.40	0.00003[a]
Yes	1536(59%)	542(52%)			78(50%)	50(40%)			1614(58%)	592(51%)		
No	1081(41%)	495(48%)			79(50%)	75(60%)			1160(42%)	570(49%)		
Administration of two or more classes of drugs[b]			229.39	<0.000001[a]			24.32	<0.000001[a]			252.99	<0.000001[a]
Yes	1736(66%)	404(39%)			110(70%)	51(41%)			1846(67%)	455(39%)		
No	881(34%)	633(61%)			47(30%)	74(59%)			928(33%)	707(61%)		
Mood stabilizers			83.34	<0.000001[a]			10.99	0.0009[a]			111.03	<0.000001[a]
Yes	2173(83%)	720(69%)			94(60%)	50(40%)			2267(82%)	770(66%)		
No	444(17%)	317(31%)			63(40%)	75(60%)			507(18%)	392(34%)		
Number of mood stabilizers[a]			143.57	<0.000001[a]			14.65	0.0006[a]			175.97	<0.000001[a]
0	444(17%)	317(31%)			63(40%)	75(60%)			507(18%)	392(34%)		
1	1583(61%)	630(61%)			77(49%)	47(38%)			1670(60%)	680(58%)		
2	530(20%)	77(7%)			17(11%)	3(2%)			537(20%)	77(7%)		
>2	60(2%)	13(1%)							60(2%)	13(1%)		
Antidepressants			64.85	<0.000001[a]			0.97	0.32			52.93	<0.000001[a]
Yes	1363(52%)	387(37%)			114(73%)	84(67%)			1477(53%)	471(41%)		
No	1254(48%)	650(63%)			43(27%)	41(33%)			1297(47%)	691(59%)		

(Continued)

Table 1. (Continued)

Socio-demographic and clinical variables	Patients with at least one side effect in the STEP-BD sample (*n*=2617)	Patients with no side effects in the STEP-BD sample (*n*=1037)	χ^2 or *F*	*p*-values	Patients with at least one side effect in the COPE-BD sample (*n*=157)	Patients with no side effects in the COPE-BD sample (*n*=125)	χ^2 or *F*	*p* -values	Patients with at least one side effect in the global sample (*n*=2774)	Patients with no side effects in the global sample (*n*=1162)	χ^2 or *F*	*p* -values
Number of antidepressants			66.25	<0.000001[a]			3.48	0.17			55.63	<0.000001[a]
0	1254(48%)	650(63%)			43(27%)	41(33%)			1297(47%)	691(59%)		
1	1103(42%)	324(31%)			89(57%)	73(58%)			1192(43%)	397(34%)		
2	242(9%)	58(6%)			25(16%)	11(9%)			267(10%)	69(6%)		
>2	18(1%)	5(<1%)							18(1%)	5(<1%)		
Antipsychotics			127.75	<0.000001[a]			11.43	0.0007[a]			132.48	<0.000001[a]
Yes	1162(44%)	251(24%)			87(55%)	44(35%)			1249(45%)	295(25%)		
No	1455(56%)	786(76%)			70(45%)	81(65%)			1525(55%)	867(75%)		
Number of antipsychotics			132.84	<0.000001[a]			12.40	0.002[a]			136.25	<0.000001[a]
0	1455(56%)	786(76%)			70(45%)	81(65%)			1525(55%)	867(75%)		
1	1083(41%)	245(24%)			71(45%)	39(31%)			1157(42%)	284(24%)		
2	79(3%)	6(<1%)			16(10%)	5(4%)			92(3%)	11(1%)		
Anxiolytics			50.12	<0.000001[a]			0.98	0.32			29.28	<0.000001[a]
Yes	652(25%)	147(14%)			102(65%)	74(59%)			754(27%)	221(19%)		
No	1965(75%)	890(86%)			55(35%)	51(41%)			2020(73%)	941(81%)		
Number of anxiolytics			50.94	<0.000001[a]			2.16	0.34			29.47	<0.000001[a]
0	1965(75%)	890(86%)			55(35%)	51(41%)			2020(73%)	941(81%)		
1	616(24%)	142(14%)			71(45%)	57(45%)			687(25%)	199(17%)		
2	36(1%)	5(<1%)			31(20%)	17(14%)			67(2%)	22(2%)		

well as patients taking a higher number of such drugs as compared with those taking a lower number, had a higher likelihood of experiencing side effects (Table 1). Furthermore, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs (Table 1). Multivariate analyses confirmed that mood stabilizers, antidepressants, antipsychotics and anxiolytics were all independent predictors of experiencing at least one side effect.

On the other hand, in the COPE-BD sample, associations were found only between total side effects and the use and the number of mood stabilizers and antipsychotics. In particular, patients taking as compared with those not taking antipsychotics and mood stabilizers, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing side effects (Table 1). Furthermore, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs (Table 1). Following multivariate analyses, however, none of these associations remained (Table 2).

Secondary outcome measures

Effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on total side effects in the global sample. In the global sample, associations were observed between the use and the number of mood stabilizers, antipsychotics, antidepressants and anxiolytics and total side effects. In particular, patients taking as compared with those not taking such drugs, as well as patients taking a higher number of such drugs as compared with those taking a lower number, had a higher likelihood of experiencing side effects (Table 1). Furthermore, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs (Table 1). Multivariate analyses confirmed that mood stabilizers, antidepressants, antipsychotics and anxiolytics were all independent predictors of experiencing at least one side effect (Table 2).

Effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on psychic side effects. In the STEB-BD sample, several associations were observed between the use and the number of psychotropic drugs and psychic side effects. In particular, patients taking as compared with those not taking these drugs, as well as patients taking a higher number of these drugs as compared with those taking a lower number or not taking these drugs, had a higher likelihood of experiencing psychic side effects (Supplementary Material, Table 2). Furthermore, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. Following multivariate analyses, the only associations that were maintained were those with antipsychotics and with anxiolytics (Table 2). Findings in the global sample mirrored those observed in the STEP-BD sample (Table 2 and Supplementary Material, Table 2).

On the other hand, in the COPE-BD sample, associations were only found between the use and the number of antipsychotics and psychic side effects. In particular, patients taking as compared with those not taking antipsychotics, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing psychic side effects (Supplementary Material, Table 2). In addition, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. However, following multivariate analysis, the only association that remained was that between psychic side effects and antipsychotics (Table 2).

Effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on neurologic side effects. In the STEB-BD sample, associations were observed between the use and the number of psychotropic drugs under investigation in this study and neurologic side effects. In particular, patients taking as compared with those not taking all such drugs, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing neurologic side effects (Supplementary Material, Table 3). In addition, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. Following multivariate analyses, the only associations that were maintained were those with antipsychotics, mood stabilizers and with anxiolytics (Table 2). Aside from the lack of association between anxiolytics and neurologic side effects, findings in the global sample mirrored those observed in the STEP-BD sample (Table 2 and Supplementary Material, Table 3).

On the other hand, in the COPE-BD sample associations were only found between the use and the number of mood stabilizers and neurologic side effects. In particular, patients taking as compared with those not taking mood stabilizers, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing neurologic side effects (Supplementary Material, Table 3). In addition, similarly to what was already observed above, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. Following multivariate analyses, the only association that was maintained was that between mood stabilizers and neurologic side effects (Table 2).

Effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on autonomic side effects. In the STEB-BD sample, associations were observed between the use and the number of psychotropic drugs and autonomic side effects. In particular, patients taking as compared with those not taking such drugs, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing side effects (Supplementary Material, Table 4). In addition, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. Following multivariate analyses, the only association that remained was that between anxiolytics and autonomic side effect (Table 2). Findings observed in the general sample substantially mirrored those observed in the STEP-BD sample. However, when multivariate analyses were performed, a significant association was observed between mood stabilizers and autonomic side effects only (Table 2 and Supplementary Material, Table 4). On the other hand, no association between any class of drugs under investigation and autonomic side effects in the COPE-BD sample was observed (Supplementary Material, Table 4).

Table 2. Multivariate analysis focusing on drugs and possible relevant stratifying variables associated with (a) all side effects, (b) psychic side effects, (c) neurologic side effects, (d) autonomic side effects and (e) other side effects in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample, in the Clinical Outcome and Psycho-Education for Bipolar Disorder (COPE-BD) sample and in the Global sample (STEP-BD+COPE-BD samples joined together). AD: antidepressants; Anx: anxiolytics; Anx dis: anxiety disorders; AP=antipsychotics; Cur dep: Current depressive episode; Diff clas: administration of two or more classes of drugs; Med dis: medical disorders; MS: mood stabilizers. [a]Significant associations.

All side effects

STEP-BD sample			COPE-BD sample			Global sample		
Clinical variables	Wald-stat	*p* -value	Clinical variables	Wald-stat	*p* -value	Clinical variables	Wald-stat	*p* -value
Curr dep ep	22.97	<0.000001[a]	Diff Clas	2.92	0.09	Cur dep ep	11.81	0.0006[a]
Med dis	9.01	0.003	MS	1.19	0.28	Med dis	15.05	0.0001[a]
Diff clas	0.63	0.42	AP	3.22	0.08	Diff clas	1.96	0.16
MS	48.59	<0.000001[a]	Age	7.34	0.007	MS	58.42	<0.000001[a]
AD	13.30	0.0003[a]				AD	9.63	0.002[a]
AP	49.31	<0.000001[a]				AP	47.00	<0.000001[a]
Anx	24.31	<0.000001[a]				Anx	11.63	0.0006[a]
Psychic side effects								
Cur dep ep	56.64	<0.000001[a]	Diff clas	0.31	0.57	Cur dep ep	48.90	<0.000001[a]
Diff clas	6.67	0.01	AP	11.45	0.0007[a]	Diff clas	7.52	0.006
MS	2.11	0.14				MS	4.88	0.03
AD	1.09	0.29				AD	0.56	0.45
AP	31.09	<0.000001[a]				AP	33.83	<0.000001[a]
Anx	19.48	0.00001[a]				Anx	12.20	0.0005[a]
Neurologic side effects								
Cur dep ep	9.72	0.002[a]	Diff clas	2.89	0.09	Cur dep ep	7.40	0.006
Med dis			MS	12.95	0.0003[a]	Med dis	8.78	0.003
Diff clas	1.64	0.19	Age	6.64	0.01	Diff clas	2.66	0.10
MS	47.75	<0.000001[a]				MS	58.03	<0.000001[a]
AD	3.77	0.05				AD	2.73	0.09
AP	11.91	0.0005[a]				AP	9.71	0.002[a]
Anx	16.75	0.00004[a]				Anx	7.74	0.005
Age	5.48	0.02				Age	5.73	0.02
Autonomic side effects								
Cur dep ep	26.55	<0.000001[a]				Cur dep ep	18.71	0.00001[a]
Anx disord	3.39	0.07				Anx disord	7.28	0.007
Med dis	17.16	0.00003[a]				Med dis	18.75	0.00001
Dif clas	1.27	0.26				Dif clas	1.10	0.29
MS	6.02	0.01				MS	10.58	0.001[a]
AD	4.97	0.03				AD	5.20	0.02
AP	2.28	0.13				AP	3.18	0.07
Anx	16.81	0.00004[a]				Anx	6.24	0.01
Other side effects								
Cur dep ep	25.92	<0.000001[a]				Cur dep ep	13.73	0.0002[a]
Anx dis	3.91	0.05				Anx disord	5.79	0.02
Med dis	12.25	0.0004[a]				Med dis	17.47	0.00003[a]
Diff clas	11.24	0.0008[a]				Dif clas	4.72	0.02
AD	4.20	0.04				MS	3.61	0.06
AP	10.48	0.001[a]				AD	3.90	0.05
Anx	5.02	0.03				AP	11.88	0.0005[a]
						Anx	0.93	0.33

Table 3. Effects of antipsychotics and mood stabilizers on single psychic and neurologic side effects respectively in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and the Clinical Outcome and Psycho-Education for Bipolar Disorder (COPE-BD) samples. [a]Significant associations.

Psychic side effects				
	Patients taking antipsychotics (*n*=1413)	Patients not taking antipsychotics (*n*=2241)	χ^2	*p* -values[a]
STEP-BD sample				
Sedation				
Yes	496(35%)	409(18%)	131.86	<0.000001
No	917(65%)	1832(82%)		
	Patients taking antipsychotics (*n*=131)	Patients not taking antipsychotics (*n*=151)	χ^2	*p* -values[a]
COPE-BD sample				
Sedation				
Yes	17(13%)	5(3%)	9.11	0.002
No	114(87%)	146(97%)		
Concentration difficulties				
Yes	29(22%)	13(9%)	10.13	0.001
No	102(78%)	138(91%)		
Asthenia/increased fatigability				
Yes	35(27%)	19(13%)	9.05	0.002
No	96(73%)	132(87%)		
Neurologic side effects				
	Patients taking mood stabilizers (*n*=2893)	Patients not taking mood stabilizers (*n*=761)	χ^2	*p* -values[a]
STEP-BD sample				
Tremors				
Yes	619(21%)	49(6%)		
No	2274(79%)	712(94%)	90.48	<0.000001
	Patients taking mood stabilizers (*n*=144)	Patients not taking mood stabilizers (*n*=138)	χ^2	*p* -values[a]
COPE-BD sample				
Tremors				
Yes	16(11%)	2(1%)	8.88	0.002
No	128(89%)	136(99%)		

Effects of mood stabilizers, antidepressants, antipsychotics and anxiolytics on other side effects. In the STEP-BD sample, associations were observed between the number of mood stabilizers and the use and the number of antipsychotics, antidepressants and anxiolytics, and other side effects. In particular, patients taking as compared with those not taking such drugs, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing other side effects (Supplementary Material, Table 5). In addition, patients taking two or more classes of drugs were more likely to experience side effects as compared with patients treated with a single class of drugs. Following multivariate analyses, the only associations that remained were those between antipsychotics, the number of classes of drugs, and other side effects (Table 2). Again, findings observed in the general sample substantially mirrored those observed in the STEP-BD sample, the lack of association between the mood stabilizers and other side effects being the only notable difference (Table 2 and Supplementary Material, Table 5). On the other hand, no association between any class of drugs under investigation and other side effects in the COPE-BD sample was observed (Supplementary Material, Table 5).

Effect of drugs associated with class-specific side effects in both studies on single class-related side effects. As reported above, the only two associations that were replicated in both samples were those between the use of antipsychotics and psychic side effects and the use of mood stabilizers and neurologic side effects (Supplementary Material, Tables 2 and 3). As a consequence, we explored the effect of antipsychotics on available single psychic side effects as well as of mood stabilizers on available single neurologic side effects in both samples independently.

Pertaining to psychic side effects, an association was observed between the use of antipsychotics and sedation in both samples

Table 4. Specific side effects associated with psychic and neurologic side effects in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP–BD) and the Clinical Outcome and Psycho–Education for Bipolar Disorder (COPE–BD) samples stratified according to specific mood stabilizers and antipsychotics.

Drugs in the STEP–BD sample	Patients experiencing sedation *n* (row %)	Patients not experiencing sedation *n* (row %)	χ^2 or *F*	*p* –values	Drugs in the COPE–BD sample	Patients experiencing sedation *n* (row %)	Patients not experiencing sedation *n* (row %)	χ^2 or *F*	*p* –values
Psychic side effects									
Aripiprazole (*n*=67)	24 (36%)	43 (64%)	19.02	0.008	First generation antipsychotics	2 (29%)	5 (71%)	3.78	0.58
Clozapine (*n*=17)	8 (47%)	9 (53%)			(*n* =7)	2 (8%)	23 (92%)		
First generation antipsychotics (*n*=43)	11 (26%)	32 (74%)			Olanzapine (*n* =25)	3 (8%)	34 (92%)		
Olanzapine (*n*=496)	188 (38%)	307 (62%)			Quetiapine (*n* =37)	6 (18%)	27 (82%)		
Quetiapine (*n*=352)	122 (35%)	230 (65%)			Risperidone (*n* =33)	1 (20%)	4 (80%)		
Risperidone (*n*=272)	72 (26%)	200 (74%)			Other antipsychotics (*n* =5)	3 (14%)	18 (86%)		
Ziprasidone (*n*=81)	38 (47%)	43 (53%)			Two or more antipsychotics (*n* =21)				
Two or more antipsychotics (*n*=82)	32 (39%)	60 (61%)							
–	–	–							
						Patients experiencing concentration difficulties *n* (row %)	Patients not experiencing concentration difficulties *n* (row %)		
					First generation antipsychotics	4 (57%)	3 (43%)	7.39	0.19
					(*n* =7)	5 (20%)	20 (80%)		
					Olanzapine (*n* =25)	6 (16%)	31 (84%)		
					Quetiapine (*n* =37)	8 (24%)	25 (76%)		
					Risperidone (*n* =33)	0 (0%)	5 (100%)		
					Other antipsychotics (*n* =5)	1 (20%)	4 (80%)		
					Two or more antipsychotics (*n* =21)				
–	–	–				Patients experiencing increased fatigability *n* (row %)	Patients not experiencing increased fatigability *n* (row %)		
					First generation antipsychotics	4 (57%)	3 (43%)	6.24	0.28
					(*n* =7)	5 (20%)	20 (80%)		
					Olanzapine (*n* =25)	7 (19%)	30 (81%)		
					Quetiapine (*n* =37)	11 (33%)	22 (67%)		
					Risperidone (*n* =33)	1 (20%)	4 (80%)		
					Other antipsychotics (*n* =5)	7 (33%)	(14 (67%)		
					Two or more antipsychotics (*n* =21)				
Neurologic side effects									
Carbamazepine (*n*=93)	10 (11%)	82 (89%)	199.09	<0.000001	Carbamazepine (*n* =6)	0 (0%)	6 (100%)	21.09	0.0003
Lamotrigine (*n*=434)	35 (8%)	399 (92%)			Lamotrigine (*n* =52)	2 (4%)	50 (96%)		
Lithium (*n*=837)	203 (24%)	634 (76%)			Lithium (*n* =38)	8 (21%)	30 (79%)		
Valproate (*n*=849)	128 (15%)	720 (85%)			Valproate (*n* =40)	2 (5%)	38 (95%)		
Lamotrigine (*n*=434)	35 (8%)	399 (92%)			MD combination (*n* =8)	4 (50%)	4 (50%)		
Lamotrigine+valproate (*n*=123)	34 (28%)	89 (72%)							
Lamotrigine+lithium (*n*=224)	69 (31%)	154 (69%)							
Lithium+carbamazepine (*n*=37)	9 (24%)	28 (76%)							
Lithium+valproate (*n*=192)	91 (47%)	101 (53%)							
Lamotrigine+lithium+valproate (*n*=73)	35 (48%)	38 (52%)							

(Table 3). The NNH for antipsychotic-induced sedation was six (95% confidence interval (CI) 5–7). Furthermore, associations were observed between antipsychotics and concentration difficulties as well as increased fatigability in the COPE-BD sample. Unfortunately, such side effects were not available for the STEP-BD sample. On the other hand, pertaining to neurologic side effects, the only association that could be observed in both samples was that between the use of mood stabilizers and tremors (Table 3). The NNH for mood stabilizer-induced tremors was seven (95% CI 6–8).

Effect of specific drugs or drug combinations associated with class-specific side effects in both studies on single class-related side effects. As a third set of analyses, we focused on which specific drugs were associated with side effects observed in the second set of analyses (Table 4). Pertaining to psychic side effects, we found that in the STEP-BD sample patients taking clozapine, quetiapine, zyprasidone and a combination of two or more antipsychotics were more likely to experience sedation than those taking other drugs, even though this association did not reach statistical significance. On the other, no significant association was observed in the COPE-BD sample. Pertaining to neurologic side effects, results from both the STEP-BD and the COPE-BD samples agree on the suggestion that patients treated with lithium or with combinations of two or more mood stabilizers (including lithium) had a higher likelihood of experiencing tremors as compared with patients taking other mood stabilizers.

Discussion

The aim of this study was to investigate side effects related to psychotropic drugs in two large independent samples of BD patients naturalistically treated with mood stabilizers, antidepressants, antipsychotics and/or anxiolytics. Several associations were observed.

First of all, we found that in the STEP-BD sample patients taking as compared with those not taking mood stabilizers, antipsychotics, antidepressants and anxiolytics, as well as patients taking a higher number of such drugs as compared with those taking a lower number or not taking such drugs, had a higher likelihood of experiencing side effects. A similar pattern of association was also observed in the COPE-BD sample with regard to mood stabilizers and antipsychotics. Of note, such associations remained after controlling for possible confounding variables. Overall, such results are in line with those observed in RCTs and in some previous naturalistic studies (Berk and Berk, 2003; Brooks et al., 2011; Guille et al., 2000; Miller et al., 2001; Papakostas, 2010; Rummel-Kluge et al., 2010; Uzun et al., 2010; Velligan et al., 2009).

Of higher interest are, however, the associations observed between specific classes of psychotropic drugs and specific subgroups of side effects. In particular, in both samples antipsychotic drugs were specifically associated with psychic side effects, whereas mood stabilizers were specifically associated with neurologic side effects. Side effects most commonly associated with antipsychotics were increased fatigability and concentration difficulties in the COPE-BD sample and sedation in both samples. Sedation is, indeed, a common side effect of both conventional and atypical antipsychotics usually employed for the treatment of BD (Calabrese et al., 2005; De Fruyt et al., 2012) as well as for the treatment of a number of other psychiatric disorders, such as major depression (Komossa et al., 2010), anxiety disorders (Depping et al., 2010) and psychotic disorders (Canas and Moller, 2010; Kumra et al., 2008; Lader, 1999). In addition, such side effects as concentration difficulties and increased asthenia observed in association with antipsychotics have likewise been reported in several studies (e.g. Hirschfeld, 2003; MacQueen and Young, 2003; Sharma, 1999). Note also that a qualitative look at the results of the STEP-BD sample suggests that the larger statistical significance was the one related to antipsychotics, providing further evidence to support our finding in the COPE-BD sample.

Furthermore, we observed an association between the use of mood stabilizers and neurologic side effects that was replicated in both samples. A closer inspection of this result showed, however, that such association was specifically attributable to mood stabilizer-induced tremors. In addition, a further sub-analysis showed that patients treated with lithium or with combinations of two or more mood stabilizers (including lithium) had a higher likelihood of experiencing tremors as compared with patients taking other mood stabilizers. Our findings are consistent with available evidence suggesting that rates of lithium-induced tremors could be as high as 20-65%, being more common in patients treated with two or more drugs (Gelenberg and Jefferson, 1995; Grandjean and Aubry, 2009).

Also, it is worth mentioning that the results of our study provide support for the notion that combining drugs both within the same and across different classes of drugs is associated with a higher likelihood of experiencing unwanted side effects, and this was particularly evident in the STEP-BD sample. Again, these findings are consistent with current literature on this topic (e.g. Brooks et al., 2011; Gallego et al., 2012; Lin et al., 2006; Solomon et al., 1996). Therefore, the decision to use polypharmacy should be always considered against the possibility of higher rates of psychotropic drug-related side effects. Finally, in accordance with several RCTs and naturalistic studies (e.g. (Berk and Berk, 2003; Uzun et al., 2010)), results from the STEP-BD study suggested as well that the use and the higher number of antidepressants and anxiolytics could be associated with the emergence of any kind of side effects. The extremely large sample size of the STEP-BD study, as well as the lack of replication in the COPE-BD sample suggest, however, that the overall effects of such classes of psychotropic medications could be smaller than those related to antipsychotics (psychic side effects) and mood stabilizers (neurologic side effects).

Before firm conclusions could be drawn from the results of this study, some limitations should be clearly acknowledged. First, the two samples greatly differed in terms of several socio-demographic and clinical features and could, therefore, represent different populations of BD patients. The possible confounding effects of these socio-demographic and clinical differences is unclear. Probably, the most important difference between the studies was related to the different use of psychotropic drugs in the two samples. In particular, whereas the use of psychotropic drugs in the STEP-BD sample was substantially in line with that recommended by international guidelines (Dennehy et al., 2007), the use of psychotropic drugs in the COPE-BD sample was significantly different. Such a discrepancy is in line with current evidence suggesting low adherence to existing guidelines in several naturalistic studies, possibly linked to region-specific and sample-specific needs (Bauer, 2002). It is worth mentioning, however, that the differences between the

two samples could likewise be considered as a strength rather than as a limitation of the present study. Indeed, a critical look at the results of our study shows that major findings were replicated in both samples and are allegedly not influenced by specific sample characteristics.

Second, the use of different instruments to assess side effects and the lack of information in the STEP-BD sample about several side effects investigated in the COPE-BD sample could raise concerns about the possibility of achieving a sufficiently adequate comparability between the studies. However, the replication of specific results, such as those related to psychic and neurologic side effects in both samples, provides support for the reliability of the observed findings. Moreover, the different methodological designs of the two studies and the consequent need for choosing a single time point for each patient in the STEP-BD sample does not allow us to unambiguously conclude whether the choice of different time-points would have led to different results. However, our choice has the advantage of maximizing sensitivity to the detection of side effects in the STEP-BD sample. Furthermore, a qualitative look at the results replicated in both samples provides support for the reliability of observed findings. Finally, the cross-sectional nature of our analysis does not allow us to conclude whether, and to what extent, side effects observed in our study could vary as a function of time.

In conclusion, the results of our study confirmed in a naturalistic setting the results previously reported in several RCTs, in particular the association between antipsychotic drugs and sedation and between mood stabilizers and tremors. In addition, as major findings were replicated in both samples, regardless of significant differences in terms of several socio-demographic and clinical variables, as well as study design and measurement instrument employed to investigate side effects within each study in the two samples, this suggests that our findings are robust and do not vary as a function of the characteristics of a given sample.

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Conflict of interest

Prof. Serretti is or has been consultant/speaker for: Abbott, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Italfarmaco, Janssen, Lundbeck, Pfizer, Sanofi, Servier. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen and Lundbeck. Prof. Mendlewicz is a member of the Board of the Lundbeck International Neuroscience Foundation and of Advisory Board of Servier. Dr. Chiesa, Dr. Calati, Dr. Fabbri, Dr. Sentissi and Prof. De Ronchi declare no conflict of interest.

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