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REVIEW

Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review

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Background: Uncertainty exists regarding the prevalence and clinical features associated with the practice of polypharmacy in bipolar disorder (BD), warranting a systematic review on the matter.

Methods: Three authors independently searched major electronic databases from inception till September 2015. Articles were included that reported either qualitative or quantitative data about the prevalence and clinical features associated with polypharmacy in adult cases of BD.

Results: The operative definitions of polypharmacy adopted across varying studies varied, with concomitant use of two or more psychotropic medications or use of four or more psychotropic medications at once being the most common and the most reliable, respectively. Regardless of type or current mood episode polarity of BD, prevalence rates up to 85% and 36% were found using the most permissive (two or more medications at once) and the most conservative (four or more) operative definitions for polypharmacy, respectively. Point prevalence prescription rates of one or more antidepressant or antipsychotic as part of a polypharmacy regimen occurred in up to 45% or 80% of the cases, respectively, according to the most permissive definition of polypharmacy. In contrast, lithium prescription rates ranged from 13% to 33% in BD patients receiving polypharmacy according to conservative and permissive definitions, possibly suggesting a reduced need for augmentation of combination strategies for those cases of BD with a favorable lifetime lithium response and/or long-lasting treatment as well as less likelihood of lithium response over the time most severe cases possibly exposed to a more complex polypharmacy overall.

Limitations: "Apples and oranges" bias; publication bias for most recently introduced compounds.

Conclusion: Polypharmacy is common among people with BD across varying type and mood episode phases of illness. Special population, including BD patients at high risk of familial load for suicidal behavior, solicit further research as well as the plausible "protective" role of lithium toward polypharmacy in BD. The PROSPERO registration number is CRD42014015084.

Keywords: bipolar disorder, polypharmacy, prevalence, systematic review

Introduction

Bipolar patients include an eclectic mix of ages and diagnostic categories across varying states of health, often receiving complex and long-lasting pharmacological interventions. In a community study, up to 9% of psychiatric patients received polypharmacy.[1] These rates increase to 13% in general population and an alluring 90% in general psychiatric settings.[2] Polypharmacy point prevalence rates up to 40% (according to the definition of three or more medications at once) or 18% (in case of four or more concomitant medications) have been reported for bipolar disorder (BD) cases suffering from long-lasting and/or treatment-resistant depression and receiving antidepressant drugs.[3] Furthermore, most of the available information about psychiatric

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medications comes from drug development programs that lead to registration and marketing. These programs almost invariably study the new drug in isolation vs either placebo or a comparator agent.[4] Experience with any new psychiatric medication in combination with another intervention is therefore virtually limited to a few short-term drug–drug interaction studies that are usually conducted in carefully screened young healthy volunteers.[5] Nevertheless, the practice of polypharmacy in BD represents the rule rather than the exception in the clinical setting, regardless of the current polarity of mood episode.[3,6–8] A number of reasons endorse the clinical practice of polypharmacy, with failure to achieve remission being the most common one.[9] This reflects the findings from the most comprehensive "real-world" pharmacological trial on BD patients to date, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[10] in which up to 42% of the symptomatic patients included at baseline did not achieve recovery within 2 years of follow-up, despite expert pharmacotherapy and psychotherapy.[11] Aimed at shedding light on the matter, a set of 12 useful criteria has been proposed for a rational polypharmacy, essentially focusing on pharmacokinetic and pharmacodynamics issues,[5] as previously done by other authors comparing different phases of BD.[12] Yet, it has not been investigated which bipolar patients were most exposed to polypharmacy. There is clinically sound predictive value for a past history of treatment. This is seen in cases that include resistant bipolar depression, sub- or full-threshold mixed features, rapid-cycling course, or affective temperaments (especially cyclothymic one). They represent a few potential clinical moderators of "hard-to-catch" issues for standard treatment of guidelines for BD.[13,14] Standard treatment guidelines on BD pose little or no attention overall toward the matter of polypharmacy, especially in relationship to the past history of treatment, which includes resistant bipolar depression, sub- or full-threshold-mixed features, rapid-cycling course, or affective temperaments (especially cyclothymic one), despite their clinically sound predictive value overall.[13,14] Both evidence in support of[4,15,16] and in dispute against[17–19] the practice of polypharmacy have been advocated to date. However, data about the actual prevalence and clinical correlates of the practice beyond the essential pharmacological and neurobiological premises are limited.

Therefore, we conducted a systematic review to assess the prevalence rates and clinical correlates across varying definitions of polypharmacy and varying mood phases of adulthood BD.

Materials and methods

This systematic review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (http://www.prisma-statement.org/)[20] following a registered publically available protocol (PROSPERO number: CRD42014015084).

Eligibility criteria

We limited our search to those records including adult subjects with BD, published in peer-reviewed journals. Limits activated were species: humans, language: English, and all adult: 19+, with no publication date restriction.

Information sources and search strategy

Sources of information included the following databases last accessed on September 11, 2015: PubMed/MEDLINE, Scopus, PsycINFO, EMBASE, Cochrane library, and Google Scholar. Contact with study authors was planned in advance whenever needed. The following keywords or their combination were used in the search strategy: "Bipolar Disorder" AND "polypharmacy" either in the title or in the abstract (or in the keywords, if allowed to be specified). Therefore, the adopted PubMed string was "Bipolar Disorder AND polypharmacy" (any field). Finally, the terms "polypharmacy," "polypharmacotherapy," "polypharmacology," "polytherapy," and "copharmacy" were used interchangeably across multiple databases.

Study selection

Included papers were those reporting epidemiological data about the prevalence and clinical features associated with polypharmacy in course of BD, with no restriction on etiology, bipolar type, specifiers/features, phase of illness or pharmacological and/or nonpharmacological treatment, class, dose, or duration of the pharmacological trials. Papers covering cases of polypharmacy in BD comorbid with additional disorders (either psychiatric or medical disorders/diseases) were also accounted whenever available. When a title and/or an abstract appeared suggestive for inclusion, the full-text reprint was obtained and examined to assess its relevance according to our inclusion/exclusion criteria. Excluded papers were case reports, oral communications, papers not including BD cases (multidiagnostic samples were nonetheless allowed) receiving multiple psychopharmacological treatments at once (any indication), those merely focusing on neurobiological, genetic, or pharmacological aspects of either BD or polypharmacy, those including (only) children or adolescents, or without an accurate description of the operative constructs of polypharmacy.

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Data collection process

Three authors (MF, BS, and DV) conducted a two-step literature search, examining all titles and abstracts, accessing the full texts of potentially relevant papers. On data collection and extraction, the appointed authors compared their own results with each other to reach a final consensus based on consensual inclusion and exclusion criteria. Any possible discrepancy between the principal investigators, blind to each other, was solved by consultation with three reviewing authors (ASK, DDB, and GP). Both autosearch and hand search for "type I" (duplicates among/across different databases) and "type II" (duplicate publications in different Journals/issues)[21] were performed using Thomson Reuters EndNote X7™ for Microsoft Windows™. Data were screened for the following characteristics: Participants, Interventions, Comparisons, Outcomes, and Study Design (PICOS) as well as funding sources. Specifically, the recorded variables for each article included in the review were author(s), year publication, study design, sample size, eventual follow-up or control group, sociodemographic status, concurrent psychotherapy or history of physical treatment for BD, outcome measures, conclusions, limitations, quality score, and quality differentiation.

Risk of bias in individual studies

Potential major confounding biases in the studies have been ascertained at study level focusing on the following: measurement/diagnostic bias (especially inconsistent/unreliable definitions of polypharmacy and/or lack of reliable diagnostic tools to make the diagnosis of BD), confounding bias (eg, lack of stratification and multivariate control for specific sociodemographic, vital, or clinical features), information (especially recall) bias, unrepresentativeness or inhomogeneity of the sample size or lack of control group, and selection by indication bias (nonrandom assignment of the exposure where applicable).[22]

Summary measures

Summary measures were risk ratio for cohort studies, odds ratio (OR) for case–control studies, or difference in mean values. Cohen's *d* effect sizes were reported, whenever available or anyway ascertainable.

Scoring and ranking of the studies

The assessed studies were rated for quality using the following eligibility criteria: 1) representativeness of the sample (0–1 point); 2) presence of BD patients only in the sample (0–2 points); 3) a priori study design with the goal of evaluating the epidemiology of polypharmacy in BD (0–2 points); 4) extension of the follow-up (longitudinal studies)/clinical records (retrospective studies) >1 year (0–2 points); 5) validation of the clinical diagnosis and definition of polypharmacy and the used treatment (if applicable) (0–2 points); 6) inclusion and control of all the available variables for potential confounders/effect modifiers that may had influenced outcome (if applicable) (0–2 points); 7) reliability of the information gathered for the identification of BD cases/recall bias (0–2 points); 8) accuracy of the study was to discern between manic, hypomanic, mixed, and depressive episodes in BD (0–2 points); and 9) appropriateness of the number of comorbid cases reported as results/sample size (0–2 points). Quality rating had 17 as the maximum score.

Studies were also differentiated in the following way: 1) good quality: most or all criteria being fulfilled, and even when they were not met, the study conclusions were thought to be very unlikely to alter (range: 10–17 points); 2) moderate quality: some criteria being fulfilled, and when they were not met, the study conclusions were thought to be unlikely to alter (range: 6–9 points); and 3) poor quality: few criteria fulfilled but the conclusions of the study were thought to be very likely to alter (range: 0–5 points).

Main clinical features at study

Among others, the following effect moderators were accounted for in the analysis: 1) illness duration; 2) ethnicity (in order to explore whether ethnic minorities may receive different care); 3) any kind of socioeconomic measure or a proxy for that, for example, education status; 4) a baseline psychiatric symptoms/general functioning score; 5) physical comorbidity; 6) psychiatric comorbidity; 7) differences in setting; 8) year of data collection (to reflect the time frame of introduction of different drugs, especially atypical antipsychotics); 9) geographical region; and 10) study design and duration of follow-up (taking into account that cross-sectional studies and those with shorter follow-up may have higher rates of polypharmacy, as it could be either part of cross-titration or transient).

Risk of bias across the studies

Any eventual bias affecting cumulative evidence (eg, publication bias, selective reporting within studies) was assessed through the study evaluation process and accounted in the discussion of the present manuscript.

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Results

Study selection

The search in PubMed generated 112 papers and 320 results in Scopus. Four hundred eleven additional results were obtained through search in Cochrane (n=7), PsycINFO (n=1), EMBASE (n=361), or Google Scholar (n=19 – including six edited books – out of 8,070 results initially obtained before limiting the Google Scholar search strategy to title and abstract, excluding patents or citations). Manual search allowed the identification of 23 additional results. Overall, the combined search strategy yielded a total of 843 results, of which 414 were removed after screening because they duplicated other articles. Three hundred eleven results were further screened; of those latter, 72 were excluded because they were not fully meeting the planned inclusion criteria (with a special reference to the operative definition of polypharmacy and the number of bipolar patients included). Therefore, 31 original studies were included in our qualitative analysis.[3,23–51] Figure 1 provides a synthetic flowchart of the multistep selection procedure. Overall, the combined search strategy yielded 843 results. Following screening for duplication, 414 articles were selected. On further evaluation, 311 studies were eliminated leaving 103 full-text articles. In all, 72 such articles were then excluded as they did not meet the planned inclusion criteria (especially, the operative definition of polypharmacy and the number of bipolar patients were included). Therefore, 31 original studies were included in our qualitative analysis.[3,23–51] Figure 1 provides a synthetic flowchart of a multistep selection procedure.

Quality score and quality differentiation results

Based on the quality differentiation, original studies were ranked as follows: poor (n=7, mean total score =3.5), moderate (n=13, mean total score =8.2), or good quality (n=11, mean total score =12.8). Additional details about pivotal cross-sectional, retrospective, and longitudinal studies have been outlined in Tables 1–3, respectively.

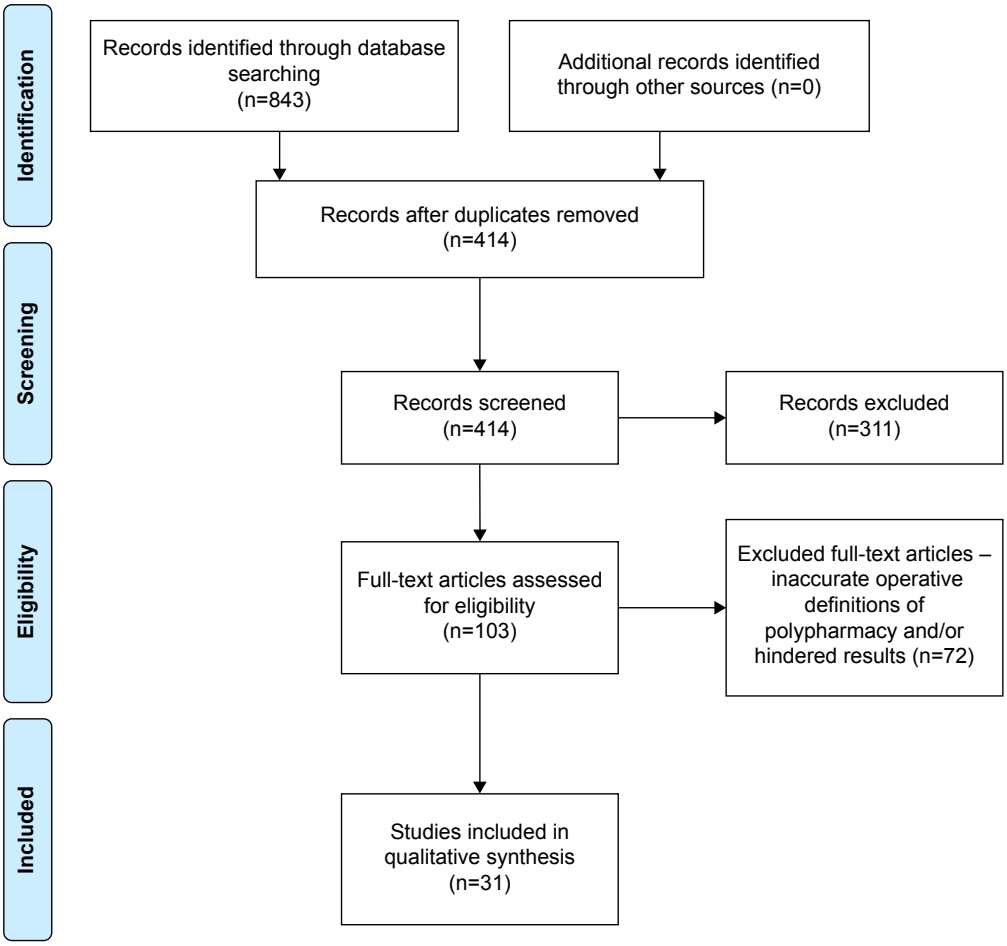

Figure 1 Adapted PRISMA 2009 flow diagram.

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Table 1 Essential cross-sectional evidence

Author	Aim/hypothesis	Sample size	Main results	Conclusions	Limitations	Quality score and differentiation
Goldberg et al[3]	To investigate the prevalence rates of complex polypharmacy (defined as more than four medications for BD) and clinical features associated with different mood episode phases of BD, primarily depression, prior to entering the STEP-BD naturalistic study.[10]	N=4,025 outpatients (BD-I, n=2,666; BD-II =1,048; BD-NOS =285; cyclothymic disorder or schizoaffective bipolar disorder =36).	Use of three or more medications at once occurred in 40% of the sample; 18% of the cases received complex polypharmacy, especially if they had ever taken SGAs, had at least six lifetime depressive episode, attempted suicide, and above-average annual income.	Complex polypharmacy occurred in approximately one in five individuals with BD. Use of lithium or proven mood-stabilizer anticonvulsants was associated with lower odds or polypharmacy. Higher income was associated with antidepressant and SGA use, higher rates of polypharmacy, and greater depressive burden.	Post hoc analysis, lack of control group, limited number of drugs, lack of additional stratifications for different classes of antidepressants or lithium blood levels or potential confounders (eg, concomitant psychotherapy or environmental stressors).	I =1 II =2 III =0 IV =0 V =2 VI =0 VII =2 VIII =2 IX =2 Total =11 Overall quality = good.

Abbreviations: BD, bipolar disorder; NOS, not otherwise specified; SGA, second-generation antipsychotic; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 2 Essential retrospective studies

Author	Aim/hypothesis	Sample size	Main results	Conclusions	Limitations	Quality score and differentiation
Sachs et al[23]	To chart-review the personality traits associated with the practice of current (≥4 drugs) and/or lifetime polypharmacy (≥11) in BD.	The study included a total of 89 consecutively selected records of treatment seeking patients with a history of refractory BD (F:M =48:41).	According to the NEO Five Factor Personality Inventory,[67] the patients with lower scores on "openness" had significantly more current psychotropic medication use compared to those cases with higher openness scores (3.7±1.9 vs 2.8±1.8; $P \leq 0.05$). Similarly, the patients with lower extraversion (21.8±8.9 vs 25.4±7.6, $P \leq 0.05$) and lower conscientiousness (21.9±8.2 vs 27.9±8.2, $P \leq 0.05$) had the highest lifetime medication use.	Low levels of openness, extraversion, and conscientiousness may be associated with higher rates polypharmacy. Further research should examine whether the duration of exposure to an ineffective medication is correlated to reluctance to discontinue ineffective agents.	Small sample size and selection bias. Lack of additional stratification for in- vs outpatient cases, type, and mood state of BD.	I =0 II =2 III =2 IV =2 V =2 VI =0 VII =0 VIII =0 IX =0 Total =8 Overall quality = moderate.
Weinstock et al[27]	To chart-review the rates of complex polypharmacy (≥4 psychotropic and nonpsychotropic drugs at once) in BD-I cases.	The sample included a total of 230 BD-I inpatients across different mood episode polarity were.	Overall, complex polypharmacy was documented in 82 (36%) of the cases. Patients reported taking an average of 3.31±1.46 psychotropic and 5.94±3.78 nonpsychotropic medications.	Data highlighted the high medication burden experienced by patients with BD, especially those BD-I inpatients who are acutely symptomatic.	Relatively small sample size and selection bias.	I =0 II =2 III =2 IV =2 V =2

(*Continued*)

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Table 2 (*Continued*)

Author	Aim/hypothesis	Sample size	Main results	Conclusions	Limitations	Quality score and differentiation
			Those cases receiving complex polypharmacy were significantly more likely to be women and to be prescribed with antidepressants, benzodiazepines, and stimulants, even after controlling for mood episode polarity. Lithium was prescribed as part of polypharmacy in 13% of the cases.			VI =2 VII =0 VIII =2 IX =1 Total =13 Overall quality = good.
Hung et al[28]	The Taiwanese Nationwide Psychiatric Inpatient Medical Claims (2000–2007) were used to examine prescription for mood stabilizers, antipsychotics, and antidepressants among recently discharged patients with BD. Operative definition of polypharmacy was two or more psychotropic medications.	Out of 5,449 BD patients, 5,155 (95%) were BD-I. Among them, n=2,923 (57%) presented with a manic episode, 1,076 (21%) depressed episode, 768 (15%) mixed episode, and 370 (7%) unspecified episode.	For 3,853 (71%) patients, prescriptions involved between-class polypharmacy, and for 941 (17%), prescriptions contained within-class polypharmacy.	Mood stabilizers accounted for a majority of polypharmacy among hospitalized patients, which rates were particularly high in case of between-class prescriptions. As prompted out by the authors themselves, this is contrast to the usual finding reported by studies carried on outpatient samples of BD, especially BD-II women, whereas antidepressants are often prescription in the context of polypharmacy.	Almost only BD-I manic inpatients were included. Permissive criterion for polypharmacy (yet accurate distinction between within- and between-class polypharmacy prescriptions).	I =1 II =2 III =2 IV =2 V =2 VI =0 VII =0 VIII =0 IX =0 Total =9 Overall quality = moderate.
Baek et al[29]	To retrospectively assess the pattern of pharmacotherapy by episode type in Korean BD patients and rates of concordance with varying international standard treatment guidelines.	The sample included BD-I cases (n=990; of whom, n=480 being currently manic inpatients, n=113 being depressive inpatients, and n=397 being outpatients) and BD-II cases (total n=457, of whom depressive inpatients were n=190 and outpatients were n=267).	The overall concordance rate of prescriptions for manic inpatients to the guidelines was higher and relatively more consistent (43.8%–48.7%) compared to that for depressive inpatients (18.6%–46.9%).	Polypharmacy was a common reason of nonconcordance toward varying treatment guidelines for BD, especially for those BD-II depressed patients receiving SGA(s) too.	Retrospective design of the study; partial control for potential confounding factors.	I =1 II =2 III =1 IV =2 V =0 VI =0 VII =1 VIII =2 IX =1 Total =10 Overall quality = good.

Abbreviations: BD, bipolar disorder; NOS, not otherwise specified; F, female; M, male; SGA, second-generation antipsychotic.

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Table 3 Essential prospective studies

Author	Aim/hypothesis	Sample size	Main results	Conclusions	Limitations	Quality score and differentiation
Haeberle et al[25]	To longitudinally follow European inpatients with a diagnosis of bipolar depression over a 15-year follow-up period (1994–2009).	A total 2,246 inpatients, both sex and age 18 or older were included in the present study.	Antidepressants were the most frequently prescribed class of drugs given in combination. Olanzapine plus fluoxetine combination was found to be prescribed only in very few patients, as it was the case for bupropion (which may reflect a differential prescription trend compared to North America within the period at study). Quetiapine was found to be the second most frequently prescribed substance for bipolar depression during the period of 2006–2009.	Overall, the present study showed that multiple combinations of psychotropic drugs is routinely prescribed in the clinical routine, including antidepressant, despite their controversial role in bipolar depression. The trend of second-generation antipsychotic combinations was also steadily increasing over the time within the covered period of time. Only 337 (15%) patients received monotherapy at time of assessment, with virtually none of them being medication free at time of hospitalization. Finally, lithium was the less common drug used in combination with any other class of substance (n=741 or 33% of the cases).	Permissive operative definition of polypharmacy (two or more class of psychotropic substances). Lack of additional demographic or clinical stratifications, including BD type.	I =1 II =2 III =1 IV =2 V =0 VI =0 VII =1 VIII =2 IX =1 Total =10 Overall quality = good.
Bauer et al[34]	To prospectively document the naturalistic prescription trends of BD patients in the USA, Germany, Canada, and elsewhere.	Data on 450 cases of BD were collected over a period of approximately 6 months. BD-I cases were n=272 (60%), BD-II n=157 (35%), and BD-NOS =17 (5%).	Polypharmacy (namely the concomitant use of at least two psychotropic medications of either the same or different classes) was recorded in up to 75% of the cases. Specifically, sustained polypharmacy regarded 353 (78.4%) of patients for at least ≥50% of days. Overall mean follow-up was 222 days.	Overall, most of the patients received mood-stabilizer drugs. Yet, though most patients were receiving polypharmacy, there were no predominant drug regimens even among those taking stable combinations. Most patients with stable combinations took a relatively small number of drugs daily.	No stratification was documented for current mood phase of BD.	I =1 II =2 III =2 IV =2 V =1 VI =1 VII =0 VIII =2 IX =0 Total =11 Overall quality = good.
Bauer et al[51]	To analyze the regularity in daily dosage of antidepressants taken by BD patients and factors associated with irregularity.	The sample included 144 BD patients: BD-I, n=67; BD-II, n=65; and BD-NOS, n=10. Females were n=108 (or 75% of the sample). Polypharmacy was defined as the use of two or more psychotropic drugs at once. Regularity was measured using the ApnEn, which is the tendency that values within a time series remain the same on the incremental comparisons.[76]	Total number of psychotropic medications was significantly associated with irregularity (P=0.005), as it was "pill burden" (P=0.005), and depression (P=0.015), Neither the percentage of days missing doses nor the drug holidays were associated with any demographic of clinical factors.	Irregularity in daily dosage is common, despite a low percentage of days missing. Daily irregularity in drug dosage may be more dependent on the individual rather than on a specific drug.	Relatively small sample size and relatively short follow-up (100 days). Permissive criterion of polypharmacy.	I =1 II =2 III =1 IV =1 V =1 VI =1 VII =0 VIII =1 IX =1 Total =9 Overall quality = moderate.

Abbreviations: BD, bipolar disorder; NOS, not otherwise specified; ApnEn, approximate entropy.

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Conceptual and operative definitions of polypharmacy across selected studies

Polypharmacy has been defined in at least 24 distinct conceptual ways, with "medication nonmatching a diagnosis" being the most commonly adopted conceptual definition,[52] capturing what could be both inappropriate therapy, that is, too many medications, and "evidence-based therapy that is inappropriate."[53] The operative definitions of polypharmacy are also elusive and/or too broad,[54–56] with the most commonly used definitions of psychiatric polypharmacy being the "use of two or more psychiatric medications in the same patient,"[2,55] rather than "use of two or more medications of the same class or equivalent pharmacologic action to treat the same condition [BD]."[57] Nonetheless, "current use of four more psychotropic medications at once" was the most reliable operative definition for "complex polypharmacy" across the most pivotal studies.[3,23,27,40,42]

Prevalence rates of polypharmacy in BD

A post hoc[3] report based on the baseline data of the STEP-BD study[10] indicated that only 12% of the patients (n=472 out 4,035) were taking none of the accounted medication at study entry, in contrast to 839 (21%) taking one vs 1,130 (28%) receiving two medications vs 883(22%) on three vs 711 (18%) taking four or more medications (complex polypharmacy). Of 2,159 females (53.5% of the total sample), 21% of whom (n=446) were received complex polypharmacy. With respect to the diagnostic type of BD, 2,666 patients were BD-I, of whom, 510 received complex polypharmacy, 2,156 received less than four medications; 1,084 were BD-II (complex polypharmacy, n=171 vs 913 not receiving complex polypharmacy); and 285 BD-not otherwise specified (NOS) cases, of whom just 30 received complex polypharmacy vs 255 who did not.

The operative definition of complex polypharmacy adopted for the STEP-BD post hoc[3] was modified by independent authors conducting a chart-review study on 230 BD-I patients (of whom, 134 or 58% females) admitted to an inpatient or partial hospitalization, herein encompassing all classes of psychotropic and nonpsychotropic medications in order to better reflect routine clinical prescriptions for BD patients.[27] In all, 186 of the cases (81% of the total sample) received complex polypharmacy, while 122 (53%) reported taking medication for nonpsychiatric purposes. Polarity of mood episode on admission was as follows: depressed, n=85 (37%); manic, n=96 (42%); mixed state, n=44 (19%); and unspecified, n=5 (2%). Among those treated with pharmacotherapy for BD, patients reported taking an average of 3.31±1.46 psychotropic medications at the time of hospitalization. Average total medication usage (including both psychotropic and nonpsychotropic medications) was 5.94±3.78. One hundred twenty-six cases (55% of the sample) reported taking three or more psychotropic medications at the time of hospitalization, and 82 cases (36%) of the study met the operational criteria for complex polypharmacy. This figure represents 44% of those receiving any pharmacotherapy for BD at the time of hospital admission. Overall, even after accounting for 20% of patients who were not engaged in any pharmacologic treatment prior to hospitalization, 55% were on three or more psychotropic medications at the time of hospital admission and 36% were on four or more. The latter figure is exactly double than the rate reported from the outpatient STEP-BD sample,[3] although more consistent with rates of polypharmacy reported in voluntary BD registries.[41] Concordant with previous reports,[58,59] additional analyses carried out by Weinstock et al[27] revealed that the average number of prescriptions almost doubled (from 3.3 to 5.9) when both psychotropic and nonpsychotropic medications were taken into account. The authors themselves also acknowledged that the discrepancy seen with respect to the STEP-BD post hoc report[3] may be attributable to different operational criteria for complex polypharmacy, differential settings, and proportion of BD-I cases.

Data from the Arzneimittelüberwachung in der Psychiatrie (AMSP) European drug surveillance program[60,61] involving 2,246 cases of bipolar depression followed over a 16-year period (1994–2009)[25] just relied on a "permissive" operative definition of polypharmacy, namely the use of two or more class of psychotropic substances. The prevalence rates of polypharmacy in European patients were therefore strikingly high, with almost 85% of the cases receiving polypharmacy in contrast to only 337 cases (or 15% of the total) receiving monotherapy (herein defined as the use of antidepressants or antipsychotics or anticonvulsants or lithium, including within-class prescriptions). Data about the practice of complex polypharmacy in European cases experiencing a current bipolar depressive episode were nonetheless made available by a 2012 report based on 2,231 inpatients (unspecified subtypes proportions) followed up in the context of the AMSP program between 1994 and 2009, which documented 137 patients (6.4% of the total) treated with at least four different psychotropic drugs at once, with rates steadily increasing, especially after year 2006.[33] Data about the practice of polypharmacy in Eastern European and Middle East patients just rely on post hoc cross-sectional analysis of the baseline records of a large (n=894) prospective

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study carried on manic patients prescribed with olanzapine (n=569 or 63.64%) or not (n=325 or 36.35%). While these data reflect a special population at study, the rates of polypharmacy were nonetheless very high (n=719 or 80.4%), although the authors adopted a permissive criterion of two or more psychotropic drugs at once.[31] Slightly lower prevalence rates in manic patients were also documented in Taiwanese inpatients approximately assessed within the same period (years 2000–2007). Specifically, out of 5,449 BD patients, 5,155 (95%) were BD-I cases, of whom 2,923 (57%) presenting with a manic episode at the time of hospitalization, 1,076 (21%) with depressed episode, 768 (15%) mixed episode, and 370 (7%) unspecified episode. Between-class vs within-class polypharmacy (according to the permissive criterion of two or more psychotropic drugs at once) occurred in 3,853 (71%) vs 941 (17%) patients, respectively.[28]

Prescription trends and main clinical features associated with polypharmacy in BD

Quality receiver–operating characteristics post hoc analysis of the baseline records of the STEP-BD study[3] also revealed that BD subjects had a 64% risk for receiving complex polypharmacy if they had ever taken any second-generation antipsychotic (SGA) drug, had six or more lifetime depressive episodes, ever attempted suicide (complex polypharmacy cases, n=686, vs noncomplex polypharmacy cases, n=1,105; $P \leq 0.0001$; Cohen's d=0.05), and had an annual income of US$75,000 or higher (complex polypharmacy cases, n=158, vs noncomplex polypharmacy cases, n=747; P= nonsignificant [ns]; d=0.00). In contrast, complex polypharmacy was least often associated with lithium (n=41 vs 225 receiving lithium but not complex polypharmacy; d=0.03), divalproex (251 vs 934 noncomplex polypharmacy cases; d=0.11), and carbamazepine (219 vs n=548 noncomplex polypharmacy cases; d=0.13), whereas complex polypharmacy was most often associated with SGA use (complex polypharmacy cases, n=482, vs noncomplex polypharmacy cases, n=780; d=0.74), with antidepressants (684 vs n=1,251 noncomplex polypharmacy cases; d=0.78 – which is actually the largest effect size reported by the authors in their analyses). Contrary to expectations, a history of psychosis (complex polypharmacy cases, n=96, vs noncomplex polypharmacy, n=309; P=0.001; d=0.02), age at onset (complex polypharmacy mean age =16.4±3.3 vs noncomplex polypharmacy mean age of onset of 16.2±3.6; P=ns; d=0.03), BD-I vs BD-II subtype (no contrasts, P-value or d value reported), prior to hospitalization (no contrasts, P-value or d value reported), current illness state (no contrasts, P-value or d value reported), and history of substance use disorder (SUD) (complex polypharmacy, n=84, vs noncomplex polypharmacy, n=461; P=ns; d=0.05) did not significantly alter the risk profiles for receiving complex regimens, although concerns about the chance of a Berkson's bias could be raised in these regards. Accounting of additional psychotropic and nonpsychotropic medications beyond the sole, seven-core medications regarded by the STEP-BD study (namely lithium, divalproex, carbamazepine, lamotrigine, and other anticonvulsants without definitely established thymoleptic properties as topiramate, gabapentin; oxcarbazepine, as well as SGA or any antidepressant) allowed Weinstock et al to provide additional insights about the clinical correlates of complex polypharmacy in BD.[27] Overall, according to this latter report, those BD-I cases receiving complex polypharmacy were significantly more likely to be female, depressed, have a comorbid anxiety disorder, and have a history of suicide attempt. Conversely, those receiving complex polypharmacy were significantly less likely to be manic and present with active psychosis at the time of hospital admission. Noteworthy, given that medication decisions may be especially driven by mood episode polarity, the authors decided on a priori basis to treat mood episode polarity as a covariate in any multivariate analysis to evaluate the demographic and clinical factors associated with complex polypharmacy and patterns of specific medication use, over and above any shared variance with mood episode. Therefore, controlling for mood episode polarity, female sex, B (standard error [SE])=0.58 (0.29), $\chi^2(1)=3.88$, P=0.049, OR =1.78; anxiety disorder comorbidity, B (SE)=0.72(0.32), $\chi^2(1)=5.18$, P=0.023, OR =2.05; and history of suicide attempt, B (SE)=0.79(0.34), $\chi^2(1)=5.60$, P=0.018, OR =2.21 remained significant predictors of complex polypharmacy for BD-I, whereas psychosis did not, B (SE)=–0.50 (0.32), $\chi^2(1)=2.40$, P=0.121, OR =0.61. Each psychotropic medication class was significantly associated with increased likelihood of complex polypharmacy. With respect to pattern of medication use by mood episode polarity, there was no statistically significant difference between depressed and mixed polarity patients (all P=0.11–0.94). As such, the authors combined these latter groups for purposes of comparison against patients presenting with pure mania. Use of antidepressants was significantly higher in the depressed/mixed polarity patients in comparison to patients presenting with pure mania (45% vs 20%; $\chi^2(1)=15.49$, $P<0.001$). This pattern of effects held for the use of selective serotonin reuptake inhibitors (26% vs 12%; $\chi^2(1)=7.64$, P=0.006), serotonin norepinephrine reuptake

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inhibitors (10% vs 2%; $\chi^2(1)=5.65$, $P=0.017$), and all other antidepressants (19% vs 7%; $\chi^2(1)=5.93$, $P=0.015$). Use of benzodiazepines (BDZs) was also significantly higher in the depressed/mixed polarity patients vs those presenting with mania (47% vs 33%; $\chi^2(1)=4.42$, $P=0.036$), while use of all remaining medications (ie, lithium, anticonvulsants, antipsychotics, stimulants, and hypnotics) did not differ as a function of episode polarity (all P-values=0.08–0.90). In addition, corresponding information about the use of varying classes of antidepressants for European BD inpatients receiving polypharmacy (yet herein adopting a permissive criterion of two or more drugs within different classes at once) was provided by Haeberle et al in 2012.[25] Olanzapine plus fluoxetine combination was found to be prescribed only in very few patients, as it was the case for the norepinephrine dopamine reuptake inhibitor bupropion, also possibly due to different drug policies and approval dates compared to the USA, despite the SGA quetiapine was found to be the second most frequently prescribed adjunctive therapy for bipolar depression during the period covered by the study, years 2006–2009, whereas lithium was the less common drug used in combination with any other class of substance (n=741 or 33% of the cases).[25] Owing to evidence pointing out that less than one-third of BD patients in the USA and about half of those in Europe received monotherapy,[3,62–65] Bauer et al planned a long-term naturalistic study in which patients with BD self-recorded mood, sleep, and drugs taken daily over a period of ~6 months with the ultimate aim to further characterize the drug treatment patterns in 450 BD cases. Of these latter BD cases, 272 were BD-I cases (60%), 157 BD-II (35%), and 17 BD-NOS cases (5%). Noteworthy, the study adopted a permissive operative criterion for polypharmacy defined as the use of two or more psychotropic drugs at once.[34] Drug load was measured using the methodology developed by the World Health Organization (WHO) based on a measure of equipotency known as the defined daily dose.[66] Overall, 315 or 70% of the cases resided in the USA; n=53 or 11.8% resided in Germany; n=45 or 10% resided in Canada; and 37 or 8.2% resided elsewhere. Enrolled patients returned a total of 99,895 days of data (mean 222.0 days), with the most frequently taken drugs being mood stabilizers and 353 patients (78.4% of the total) taking a stable drug combination for half of days or longer. The majority of patients were taking polypharmacy, including 75% of those with a stable combination. Only a small number of drugs were commonly taken within each medication class, but there were a large number of unique drug combinations: 52 by medication class and 231 by specific drugs. Eighty percentage of patients with a stable combination were taking three or less drugs daily, although no specific report was documented in relationship with polypharmacy and lifetime hospitalization. Two previous chart-review studies on 457 BD-I cases suggested a positive correlation between the total number of current psychotropic medications and the number of hospitalization for depressive episodes, though not with suicidal attempt, neither lithium nor carbamazepine use in case of hospitalization due to mania.[40,41] Finally, while most cross-sectional and longitudinal studies on the relationship between polypharmacy and the clinical features and/or prescription trends primarily focused on symptomatic cases of BD, evidence focusing just on 80 euthymic patients documented that those subjects self-reporting normal mood over a period of 3 consecutive months or longer usually received a lower number of drugs compared to nonlasting cases of euthymia, though a "selection by indication bias" would be prompted out considering that those cases receiving polypharmacy may already include the most severe and possibly rapid-cycling course cases of BD.[42]

Personality features associated with polypharmacy in BD

A retrospective chart review of 89 treatment-seeking BD outpatients (F:M =48:41) assessed by the means of the revised NEO Five Factor Personality Inventory[67] about five personality dimensions, including neuroticism (the tendency to experience negative affect), extraversion (a tendency toward energy, positive emotions, and stimulation-seeking), conscientiousness (a tendency toward self-discipline and dutiful behavior), openness to experience (sometimes described as intellectual curiosity), and agreeableness (a tendency to be cooperative and compassionate) took into account 41 commonly prescribed psychotropic medications grouped in six classes (mood stabilizers, antidepressants, dopamine blockers, anxiolytic/sedative hypnotics, stimulants, and other) splitting the samples based on mean psychotropic medication use as follows: for current psychotropic medications: ≤3= low vs ≥4= high and for lifetime medications: ≤10= low vs ≥11= high. The subgroup with low openness had significantly more current psychotropic medications (3.7±1.9) than patients in the higher distribution of openness scores (2.8±1.8, $P<0.005$). There was no other comparison that reached statistical significance for either current or lifetime medications. Nonetheless, the subgroup using 18 or more lifetime psychotropic medications had significantly lower extraversion (21.8±8.9 vs 25.4±7.6, $P\leq0.005$) and lower conscientiousness (21.9±8.2 vs 27.9±8.2, $P<0.001$)

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than those reporting lifetime usage of fewer than controls. Remarkably, the authors did not examine whether the duration of exposure to an ineffective medication would be correlated to reluctance to discontinue the ineffective agent, so that at present, conclusive statement about the potential moderator effect of personality traits in BD as measured by the means of the NEO Five Factor Personality Inventory could not be drawn.

Polypharmacy in suicidal behavior bipolar patients

Although different studies also accounted for suicidal cases of BD, the only quantitative evidence specifically addressing this issue involved 169 BD outpatients (most of whom being BD-I cases, n=145 or 85.7%) and used a permissive criterion for polypharmacy (two or more psychotropic medications), which actually occurred in 142 (84%) of the cases in contrast to just 27 patients (16%) receiving monotherapy. Polypharmacy with three or more medications occurred in 31 (19%) of the cases. Overall, rapid-cycling course was seen in up to 26.9% of the cases, which is a quite high rate, especially taking into account that most of the suicidal behavior outpatients were BD-I rather than BD-II cases.

Antipsychotic drugs prescription rates and polypharmacy in BD

The evidence about the use of antipsychotic polypharmacy in BD is also scarce and prone to publication bias considering the relatively novel introduction of most SGA drugs or their latter approval for BD and/or popularity as off-label prescriptions for BD patients, which nonetheless increased over the time.[68] Also, different prescription trends for SGA vs first-generation antipsychotics (FGAs) may depend on the geographical setting and resource settings, as Eastern European BD inpatients were less frequently prescribed with SGAs in comparison to their Western counterpart, with a 2010 report documenting 23.8% of them receiving two antipsychotics vs 28.6% receiving "complex antipsychotic polypharmacy."[48] Indeed, much larger samples of BD patients prescribed with antipsychotic polypharmacy were documented by North American studies. For example, retrospective data on multistate Medicaid population for years 1998–2003 regarded 8,489 BD patients (unspecified proportion of BD subtypes), of whom 623 (7.3%) took antipsychotic polypharmacy (one or more antipsychotic drug) for at least 60 consecutive months (accountable SGAs at the time were olanzapine, quetiapine, risperidone, and the atypical antipsychotic clozapine).[44] Additionally, cross-sectional information on antipsychotic polypharmacy based on 1998 data (accounted SGAs could be olanzapine, quetiapine, risperidone, or clozapine) about US inpatients with psychotic disorders, of whom 36 were diagnosed with BD (unspecified subtypes), documented equal rates of antipsychotic polypharmacy (two or more drugs), and antipsychotic monotherapy (n=18 or 50% each group). It also documented the association of short-term treatment with multiple antipsychotics to major increase in drug exposure, adverse events, and time in the hospital, with no apparent gain in clinical benefit.[46] An updated 2008 report by Centorrino et al still based on 2004 records of antipsychotic polypharmacy in US inpatients documented very high rates of polytherapy including one antipsychotic drug (80%) or two or more antipsychotics (23%) at once for at least 3 consecutive days in the BD subset of the sample wherein BD subjects formed (n=37 out of 305 or 12.13%). Yet again, no clear-cut stratification between FGA and SGA was documented for, across varying BD subsets.[45] Concerning the antipsychotic prescribing patterns in US outpatients, a chart review of 2003–2004 data using a permissive operative definition of two or more antipsychotics involving also BD cases (n=511, no stratification of results across different BD subtypes) documented antipsychotic polypharmacy prevalence rates of 10% (53 cases), with accounted SGAs being risperidone, olanzapine, and quetiapine, although once again results were not stratified distinguishing between FGA vs SGA prescription trends.[47]

Polypharmacy in special BD populations

Little is known about the practice of polypharmacy among special population of BD, and virtually no data exist about any eventual difference in care based on ethnicity in non-US samples. Sometimes, rates have been documented in qualitative but not quantitative way, as it was the case of BD inpatients with SUD reported to receive both higher number and doses of both conventional mood stabilizers and SGAs compared to non-SUD lifetime comorbidity.[69] Only a handful of studies have nonetheless provided essential quantitative data for alternative special settings/population of BD. Our knowledge is relatively limited even with respect to the practice of polypharmacy in BD inmates. Two longitudinal 12-week studies by Kamath et al documented strikingly high prevalence rates for polypharmacy (use of three or more psychotropic medications at one) in 84% of the cases (out of a total sample of 40 BD-I or BD-II cases, equal ratios for males and females)[43] urging the need for standard medication algorithms to reduce the polypharmacy in the correctional setting, with a special reference to antidepressant and antipsychotic drugs.[70] Similarly, despite the acknowledgment

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that pharmacological treatments for BD have historically been associated with neurocognitive side effects, especially in elderly subjects or otherwise possibly cognitively vulnerable subjects who would be particularly sensitive to polypharmacy,[71,72] very little is known about these subjects, including bipolar subjects with intellectual disabilities (IDs). A report on 101 BD patients (F/M, n=59/41) aged 60 and older (mean age: 68.9±7.8 years), of whom 57 (56%) BD-I and 44 (44%) BD-II cases, with an onset of first affective symptoms before age 50 in 75.6% cases, was nonetheless studied with respect to polypharmacy (two or more psychotropic medications), which was documented in 31.7% of the cases (n=32), with equal daily median number of psychotropic medications in both BD-I and BD-II cases (median =2; interquartile range =3). Interestingly enough, among other classes of psychotropic drugs, lithium was the most frequently prescribed one in BD-I and BD-II cases: 63.2% vs 43.1%, respectively.[49] Regrettably, evidence about the practice of polypharmacy in BD outpatients with ID is even less conclusive, with the only available quantitative reports on the matter failing to provide any accurate stratification of results beyond the generic statement of similar polypharmacy rates occurring in ID (n=59) and non-ID (n=16) cases (range: 24%–38%) based on the operative criterion of two or more drugs rates in the ID (n=59)[50] or relying on unrepresentative subsets of BD cases,[73] despite the widespread and controversial clinical use of polypharmacy even for BD subjects with ID.[74] Similarly, only one study about the practice of polypharmacy involving pregnant bipolar women could meet our inclusion criteria.[32] Complete retrospective data ~115 pregnancies, 75 of whom were followed throughout gestation while 40 had data for one certain gestational period, based on the Medicaid database of 5,000 women coded according to the International Classification of Diseases, Ninth Revision within years 2002–2004 indicated that the mean number of medications taken during pregnancy for manic BD-I cases was three (range: 0–10; mode =3), whereas 26.8% of the pregnant women filled prescriptions for six to ten medications during their pregnancy. Surprisingly, no dose change was made for the prescribed medications to accommodate changing metabolism across pregnancy. The most frequently prescribed psychotropic medications were from the opiate family, most likely due to comorbid diagnoses (especially SUD). However, the effects of taking multiple medications on pregnancy outcome and fetal development were unknown.[32] These findings are nonetheless compelling, especially considering that according to the clinical records of 53 fertile women with different mental illnesses (including 24 BD cases), about one-third (n=8 or 36%) were taking more than one psychotropic medication within the first trimester of an unplanned pregnancy.[75]

Polypharmacy and treatment adherence in BD

The association between polypharmacy (two or more psychotropic medications at once) and self-reported adherence with daily dose of mood stabilizer (lithium, valproate, lamotrigine, carbamazepine, or oxcarbazepine) was obtained by Bauer et al[35] for 312 BD patients (BD-I, n=198; BD-II =100; and BD-NOS =14) over a 6-month period, accounting for the mean daily number of psychotropic drugs, which was 3.1±1.6 (7.0±4.2 pills daily). No significant association was found between the daily number of medications and the daily number of pills, although the smaller the dosage of mood stabilizer taken, the higher the self-reported adherence to overall psychotropic prescriptions.[35] In order to further characterize the factors associated with irregularity of daily dosage of antidepressants in BD, Bauer et al gathered self-reported information about medication dosage and mood ratings from 144 BD patients (BD-I, n=67 or 47.2%; BD-II, n=65 or 45.8%; and BD-NOS, n=10 or 7%) who received treatment as usual (of whom, 111 were also taking a mood stabilizer).[51] Regularity was measured using the "approximate entropy" (ApnEn), which is the tendency that values within a time series and remains the same on incremental comparisons.[76] The authors documented that although the mean percentage of days with missing doses was only 18.6%, there was a wide range of regularity in the daily antidepressant dosage. Drug holiday and polypharmacy (namely the use of two or more psychotropic drugs) were also significantly associated with irregularity (P=0.005), as it was the case for "pill burden" (P=0.005), and depression (P=0.015). Neither the percentage of days missing doses nor the drug holidays were associated with any demographic or clinical factors in the sample at study, which predominantly included female cases over male ones (F:M, n=108:36 or 75% vs 25%). Interestingly enough, the authors concluded that irregularity in daily dosage may be more dependent on the individual rather than on a specific drug, despite there being no assessment of temperamental or personality traits of the involved patients over the 100-day follow-up period. Nonetheless, conclusive evidence about the association of treatment nonadherence and polypharmacy in BD remains elusive, as a 2008 report by Baldessarini et al indicated that prevalent lack of treatment at 1 year was associated with sustained mood-stabilizer adherence (subgroup, n=620), with those

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patients on lithium or lamotrigine being more often adherent than those prescribed with valproate, carbamazepine, or oxcarbazepine (nonadherent subgroup, n=1,577; uncertain cases were excluded in secondary analyses).

Polypharmacy rates and concordance with standard treatment guidelines in BD

Polypharmacy accounted for nonconcordance with varying different guidelines for the pharmacological management of BD as documented by a Korean chart review using the permissive operative criterion of two or more psychotropic medications at once.[29] The study included 1,447 BD patients, including 990 BD-I cases (of whom, n=480 being currently manic inpatients; n=113 being depressive inpatients; and n=397 being outpatients) and 457 BD-II patients (of whom, n=190 being depressive inpatients and n=267 being outpatients. The authors concluded that varying degree of concordance rates across different guidelines essentially depended on the structure of heterogeneous guidelines themselves. For example, the 2009 edition of the Canadian Network for Mood and Anxiety Treatments (CANMAT)[77] and 2010 of the Korean Algorithm for Bipolar Disorder (KMAP-BP) guidelines had identical initial strategy for mania. In the manic inpatient group, the initial treatment strategy for 317 (66.0%) of 480 patients was equally concordant with both these latter guidelines. Nonconcordant initial treatment strategies included SGA polypharmacy (22.1%), mood-stabilizer polytherapy (9.6%), and use of carbamazepine (1.9%) or typical antipsychotics (0.4%). Approximately half of concordant cases at the initial step had continued the same strategy for the entire treatment period (176 of 317, 55.5%). The concordance rate was lower for the next step in the treatment. The overall concordance rate with the CANMAT guidelines was 48.7% (234 of 480), and the concordance rate with the KMAP-BP guidelines was 43.8% (210 of 480). Mean duration to proceed to the next treatment step (adding or discontinuing medication) was ~15 days. In addition, the CANMAT guidelines provide an algorithm among bipolar depression only for bipolar I disorder (n=113). In the depressive inpatient group, only 30 cases (26.5%) were concordant with the initial treatment strategy of the CANMAT guidelines. More than half of the subjects were treated with the combination treatment, which was not included in the first step of the CANMAT algorithm. The overall concordance rate with the CANMAT guidelines was only 18.6% (21 of 113). Most nonconcordant subjects started two or more different medications concomitantly. The concordant rate for bipolar depression with the initial strategy of the KMAP-BP guidelines was 63.4% (192 of 303), as KMAP-BP included mood stabilizer plus SGA as one of the first options for bipolar depression. Nonconcordant initial treatment strategies essentially regarded SGA polytherapy and multiple mood stabilizers at once. The overall concordance rate with the KMAP-BP guidelines was 46.9% (142 of 303). When compared the concordance rate with the 2006 edition of the American Psychiatric Association (APA) practice guidelines[78] and the 2009 edition of the World Federation Societies for Biological Psychiatry (WFSBP) guidelines,[79] the overall concordance rates for mania were only 7.3% and 2.1%, respectively. The authors concluded that nonconcordance occurred mainly because lithium is not recommended as the first line because of its potentially slower onset of action, and monotherapy should always proceed in the WFSBP guidelines. Finally, concerning the treatment of acute depression, the concordance rate with the APA or WFSBP guidelines was much lower, that is, 5.6% with the APA guidelines and 11.9% with the WFSBP guidelines. This latter quantitative evidence is in line with Western reports, pointing out a major impact of polypharmacy in determining poor adherence toward standard prescription guidelines, especially in the case of antipsychotic polypharmacy in the inpatient and/or the inmate units.[36]

Discussion

Study limitations and implications and premises

Most of the limitations of the present systematic review are intrinsically related to the potential biases hampering the validity of the included studies and should be taken into account in the interpretations of the overall results presented herein. For example, given that medication decisions may be especially driven by mood episode polarity (eg, antidepressants prescribed for a depressive vs a manic episode), the fact that a number of included studies did not punctually stratify their own results using mood episode polarity as covariate in any multivariate analysis of significant univariate effect (if ever carried) should be considered. The inconsistency of the operative definitions of polypharmacy invariably affects the generalizability of the quantitative and qualitative results too, even if we strived to stratify our own results accordingly. Specifically, the ORs and risk ratios of the given studies included in the present review may differ across different studied samples according to the operative definitions of polypharmacy, sex, history of suicide attempt, associated medical and/or psychiatric clinical correlates, and Cohen's *d* effect sizes could be documented or extracted whenever possible only. Publication and measurement (namely "diagnostic

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shift") biases should also be regarded. Indeed, most of the recently introduced SGA or novel antidepressant drugs could not be assessed by previous studies. In addition, little is known about specific regional or cultural settings despite the potential impact of either cultural or pharmacoeconomic issues on prescription trends across different high resource regions,[80,81] although strikingly high prevalence rates of polypharmacy were documented even in nonhigh resource settings worldwide, especially when permissive operative criteria were adopted.[28,31,82] With respect to low-income and/or non-Western regions, even when such information was available, it often came from outdated or generic reports. For example, low rates of "affective psychosis" in contrast to "schizophrenia" cases were documented in Nigeria based on pharmacological treatment records dating back to the late 1970s.[83] Yet, much higher prevalence rates of "affective disorders" was documented in the same region by a more recent multidiagnostic study focusing on polypharmacy.[84] In this regard, we speculate that a diagnostic shift from schizophrenia to "affective disorders", in the broader sense, thus encompassing BD too, may reflect either differential settings (in- vs outpatient facilities) or the diagnostic revisions occurred within the past decades.[81,85,86] These are additional crucial issues in the interpretation of cumulative evidence on polypharmacy "in BD" obtained from studies published within a large time frame beyond the sole "regional setting" variable. Finally, it is worth mentioning that while the stringent selection criteria adopted through this qualitative and quantitative review greatly reduced the number of contributes considered of adequate quality, this systematic selection ideally emphasized just the most rigorous and clinically relevant results on the topic, which is also a critical issue for the topic at issue considering the discrepancy exiting between real-world practice and the standard treatment guidelines on the matter.

Final remarks and implications for the clinical practice

> […] Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.

This much pessimistic quote was attributed to François-Marie Arouet (1694–1778), best known by his nom de plume Voltaire. It was corroborated by the position of his countryman Philippe Pinel (1745–1826), who "was one of those physicians who reacted most strongly against the abuses of polypharmacy [multiple medications]" as René Semelaigne wrote in 1888, a later-born psychiatrist whose family had memories of Pinel.[87] This still reflects the attitude of many of modern prescribers toward BD polypharmacy.

Indeed, since 19th century, the practice of polypharmacy for what it is nowadays considered BD has spread consistently worldwide. It has been documented a tenfold increase in percentage of patients receiving three or more psychotropic medications at discharge between 1974 and 1995,[88] with much higher rates virtually occurring within the past 2 decades due to the increasing availability of novel pharmacological compounds, including antidepressant and SGA drugs, in the absence of any novel "silver bullet" drug for BD after the introduction of lithium.[7,89,90]

While a firm position either in support or against the practice of polypharmacy in BD is out of the scope (and the possibility) of the present evidence-based qualitative and quantitative synthesis, it is nonetheless worth noting that polypharmacy for BD is an extremely common scenario, often poorly, scientifically sound. Not all of the polypharmacy routine follow a pharmacological and/or diagnostic rationale or the standard guidelines, with the ultimate risk of further burden on the patents rather than additional benefit. Thus, it is mandatory that future replication studies will expand the current knowledge about the prevalence and the clinical features of polypharmacy testing the reliability and validity of different operative definitions, ideally focusing on selective clinically sound potential moderators currently precluding any reliable quantitative extraction on the matter beyond the qualitative synthesis provided by a systematic review, with a special emphasis toward affective temperaments, history of suicidal behavior, and/or rapid cycling and mixed features, especially considering that the ultimate goal in the management of BD should be paving the ground for long-term stability (thus regarding efficacy, tolerability, sustainability, and adherence issues) rather than merely focusing on the acute phase management.

Author contributions

MF conceived the study. BS and DV assisted in study procedures. DDB, ASK, GP, and AV contributed to manuscript drafting and interpretation of the results. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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