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A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: the role of antidepressant and antipsychotic drugs

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Abstract:	The present systematic review was aimed at critically summarizing the evidence about treatment-emergent manic/hypomanic and depressive switches during the course of bipolar disorder (BD). A systematic search of the MEDLINE, EMBASE, CINAHL, Web of Science, and PsycInfo electronic databases was conducted until March 24th, 2021, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Observational studies clearly reporting data regarding the prevalence of treatment-emergent mood switches in patients with BD were considered for inclusion. Thirty-two original studies met the inclusion criteria. In the majority of cases, manic switches were analyzed; only 3 papers investigated depressive switches in type I BD. Treatment-emergent mania/hypomania in BD subjects ranged from 17.3% to 48.8% and was more frequent with antidepressant monotherapy compared to combination treatment with mood stabilizers, especially lithium, or second-generation antipsychotics. A higher likelihood of mood switch has been reported with tricyclics and a lower rate with bupropion. Depressive switches were detected in 5-16% of type I BD subjects and were associated with first-generation antipsychotic use, the concomitant use of first- and second-generation antipsychotics, and benzodiazepines. The included studies presented considerable methodological heterogeneity, small sample sizes and comparability flaws. In conclusion, many studies, although heterogeneous and partly discordant, have been conducted on manic/hypomanic switches, whereas depressive switches during treatment with antipsychotics are poorly investigated. In BD subjects, both antidepressant and antipsychotic medications seems to play a role in the occurrence of mood switches, although the effects of different pharmacological compounds have yet to be fully investigated.

Cover Letter

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March 14th, 2022

Dear Editors,

on behalf of my co-authors, I would like to submit the attached manuscript "*A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: the role of antidepressant and antipsychotic drugs*". We believe that the present systematic review has important clinical and research implications and therefore deserves publication in the European Neuropsychopharmacology.

All authors made substantial contributions to the writing of the paper and approved the final version of the article. If accepted, the paper will not be published either whole or in part elsewhere without the consent of the Publisher and all authors will disclose details of preprint posting, including DOI and licensing terms.

I confirm that the content has not been published or submitted for publication elsewhere.

We hope that this work will be of interest to yourself, your referees and to the readers of European Neuropsychopharmacology and look forward to hearing from you.

Sincerely,

Prof. Giulio Perugi

Pisa, 13/03/2023

Ref: **ENP-22-139R1**

Dear editor,
Please find enclosed a revised version of the manuscript *"A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: the role of antidepressant and antipsychotic drugs"*.

Response to Reviewers:

Reviewer 2

1. While the authors have considered the concerns raised by reviewers, and at some points added qualifying language, there do not seem to have been changes made in a consistent fashion. For instance, there is mention of adopting a consistent definition of TEM occurring within 8 weeks, yet the data shown continues to use data from studies that defined it beyond 8 weeks.

Response
In the manuscript we have provided what is the most widely accepted definition of TEM, i.e. that of ISBD. In the methods, however, we specified that our inclusion criteria required the study to have established operational criteria to define affective switch but not necessarily that the study used the ISBD criteria. Therefore, studies with time intervals longer than 8 weeks were also included and discussed in the review. However, we agree with the reviewer that more clarity is needed on this issue. Therefore, in the Discussion, we rewrote the following paragraph (pages 11-12): "The high heterogeneity in the prevalence of TEM (17-49%) may be partly attributed to the widely varying diagnostic criteria and duration of follow-ups. Indeed, according to ISBD criteria, some studies included an 8-week follow-up from the start of AD treatment or from the last change in dosage or type of AD (Ghaemi et al., 2004; Gorwood et al., 2016; Joffe et al., 2002; Valentí et al., 2012), while other studies envisaged longer observation periods (Benazzi, 1997; Berkol et al., 2019; Fornaro et al., 2018a; Goldberg and Whiteside, 2002) or did not mention specific chronological criteria to define TEM (Bottlender et al., 2004; Mundo et al., 2006). In our review, TEM was reported to be associated with a short duration of AD treatment. This is partially in contrast with previous reports claiming relative safety of AD use for bipolar depression in the short-term (Gijsman et al., 2004; Sachs et al., 2007). Nevertheless, with a view to individualized treatment that takes into account the chronic course of BD, future prospective studies should investigate manic/hypomanic episodes associated with both short-term and long-term AD use, as well as investigate other possible clinical indicators of mood destabilization associated with AD."

2. Similarly, the authors respond to review concerns about inclusion of MDD studies, yet still reflect on MDD studies in the discussion. The authors are encouraged to review the entire manuscript to ensure consistency in how reviewer concerns are being addressed.

Response
We removed the paragraph on treatment emergent mania in MDD subjects.

3. Reviewers have also raised concerns about only using naturalistic data, and the conclusions / limitations section curiously focuses on the notion of "tolerability" and "side effects" of medications being best considered within naturalistic settings, which isn't typically how treatment-emergent epsides are described.

Response

We thank the reviewer and agree with his comment. Accordingly, we revised the manuscript following his suggestions. Both at the end of the Introduction and in the discussion, we better supported our choice to include only data from observational studies, specifying their limitations and strengths.

Page 5-6: "In our opinion, the context of naturalistic, observational studies is best suited to investigate treatment-emergent episodes and the one that most reflects routine clinical practice, involving BD subjects with chronic and highly cyclical course, multiple comorbidities, and drug combinations. In addition, observational studies focus primarily on physician-assessed course characteristics and global functioning. In contrast, interventional trials usually involve highly selected subjects, short follow-up periods, and rely mainly on rating scales designed to test for short-term efficacy and side effects."

Page 16: "On the other hand, the strength of including only observational studies lies in their greater suitability to study BD course characteristics, including short- and long-term mood swings due to treatment. Indeed, naturalistic studies usually involve longer follow-up periods, broader sample inclusion criteria, and clinician-rated outcomes, thus reflecting clinical reality more closely than clinical trials. The latter, on the other hand, are often designed to test short-term efficacy and side effects through specific rating scales in highly selected BD populations."

We thank the reviewer for suggestions and assistance and hope that the manuscript is suitable for publication in its current form.

Best regards,

Giulio Perugi

A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: the role of antidepressant and antipsychotic drugs

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Contents

Abstract

The present systematic review was aimed at critically summarizing the evidence about treatment-emergent manic/hypomanic and depressive switches during the course of bipolar disorder (BD). A systematic search of the MEDLINE, EMBASE, CINAHL, Web of Science, and PsycInfo electronic databases was conducted until March 24th, 2021, according to the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (*PRISMA*) statement. Observational studies clearly reporting data regarding the prevalence of treatment-emergent mood switches in patients with BD were considered for inclusion. Thirty-two original studies met the inclusion criteria. In the majority of cases, manic switches were analyzed; only 3 papers investigated depressive switches in type I BD. Treatment-emergent mania/hypomania in BD subjects ranged from 17.3% to 48.8% and was more frequent with antidepressant monotherapy compared to combination treatment with mood stabilizers, especially lithium, or second-generation antipsychotics. A higher likelihood of mood switch has been reported with tricyclics and a lower rate with bupropion. Depressive switches were detected in 5-16% of type I BD subjects and were associated with first-generation antipsychotic use, the concomitant use of first- and second-generation antipsychotics, and benzodiazepines. The included studies presented considerable methodological heterogeneity, small sample sizes and comparability flaws. In conclusion, many studies, although heterogeneous and partly discordant, have been conducted on manic/hypomanic switches, whereas depressive switches during treatment with antipsychotics are poorly investigated. In BD subjects, both antidepressant and antipsychotic medications seems to play a role in the occurrence of mood switches, although the effects of different pharmacological compounds have yet to be fully investigated.

Keywords

Bipolar Disorder; mood switch; treatment-emergent mania; treatment-emergent depression.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating psychiatric illness characterized by recurrent depressive, hypomanic/manic, and mixed episodes (Vieta et al., 2018). Mood switch, i.e., the abrupt transition from one mood episode to another episode of opposite polarity, has long been known as a core feature of BD (Salvadore et al., 2010). With the advent of modern psychopharmacology, treatment-emergent affective switches have become an increasingly relevant clinical issue. Recently, guidelines for bipolar treatment from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) have highlighted the risk of treatment-induced manic and depressive switches in individuals with BD (Yatham et al., 2018). Indeed, antidepressants (ADs), and especially tricyclics, could trigger a hypomanic/manic or mixed episode in depressed subjects suffering from BD (Koszewska and Rybakowski, 2009; Leverich et al., 2006). On the other hand, first-generation antipsychotics might be associated with depressive switches in individuals treated for a manic or mixed episode, whereas there are still contrasting data on the risk of switches with second-generation antipsychotics (Goikolea et al., 2013; Tohen et al., 2003a).

The AD-associated transition from depression to mania has been a widely studied topic over the years. The ISBD task force defines treatment-emergent mania or hypomania (TEM) as a full syndromic hypomanic, manic, or mixed episode that lasts at least 2 consecutive days and occurs up to 8 weeks after the putative causal intervention (last treatment change) (Tohen et al., 2009). The task force recommends further consideration of including the specific treatment (i.e., AD-associated switch) if the switch emerges within less than 2 weeks. However, operational definitions of TEM and methodological assessments widely varied across studies, leading to inconsistent findings regarding the prevalence of TEM and its clinical risk factors. A recent systematic review reported a TEM prevalence of 31% in BD subjects (Fornaro et al., 2018b). However, the authors highlighted the need for more homogeneous studies that should investigate both short- and long-term affective switches.

Despite the lack of widespread agreement on the possible role of several ADs in triggering mood switches, these medications are recommended in association with a mood stabilizing therapy in depressed subjects suffering from BD, particularly those with type I BD (Pacchiarotti et al., 2013; Viktorin et al., 2014). In fact, aside from TEM, AD treatment has been associated with mixed features, dysphoria, irritability, rapid cycling, and increased suicide risk (El-Mallakh et al., 2008; Lee et al., 2013).

On the other hand, the switch from mania to depression has often been neglected by both the clinical and the research community. Indeed, few studies have explored its prevalence, as well as possible clinical and pharmacological factors associated with this particular phenomenon (Goikolea et al., 2013; Vieta et al., 2009). A depressive switch has been estimated in 13% of BD subjects at their first manic episode (Tohen et al., 2003b) and antipsychotics, mainly typical ones, seem to play a role in increasing this risk (Tohen et al., 2003a; Zarate and Tohen, 2004). Treatment-emergent depressive switch is defined as a full syndromic depressive episodes lasting at least 1 week and occurring up to 8 weeks from the last change in treatment (Tohen et al., 2009). As for TEM, the ISBD task force recommends referring to an antipsychotic-associated switch if it occurs within less than 2 weeks of starting treatment. As for acute bipolar depression, pharmacological treatment of acute mania and mixed states needs to be chosen carefully in order to reduce the risk of a depressive switch (Vieta, 2005).

Based on these premises, the primary objective of the present systematic review is to assess the prevalence of treatment-emergent mood switches in samples of subjects with BD evaluated in a naturalistic setting. A second objective is to investigate the possible clinical correlates that distinguish BD subjects with treatment-emergent switches from those not presenting this condition. In our opinion, the context of naturalistic, observational studies is best suited to investigate treatment-emergent episodes and the one that most reflects routine clinical practice, involving BD subjects with chronic and highly cyclical course, multiple comorbidities, and drug combinations. In addition, observational studies focus primarily on physician-assessed course characteristics and global

functioning. In contrast, interventional trials usually involve highly selected subjects, short follow-up periods, and rely mainly on rating scales designed to test for short-term efficacy and side effects.

2. Methods

This review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009; Page et al., 2021). Search methods and results are highlighted in Figure 1. A study protocol was registered with PROSPERO and published a priori (CRD42021233638).

2.1. Search strategy

First, a comprehensive computerized literature search of five bibliographical databases – MEDLINE, EMBASE, CINAHL, Web of Science, and PsycInfo – was performed from inception to March 24th, 2021, cross-checking the obtained references. Detailed search strings are provided in the *Supplementary material S1* that accompanies the online edition of this article. Secondly, we conducted a manual search of the reference lists of included articles to supplement the electronic searches (see references of studies excluded after full-text review and reasons for exclusions in the *Supplementary material, Table 1*).

Two independent investigators (MB and GM) screened title/abstracts of retrieved references for eligibility, evaluated the full texts of potentially eligible articles, and extracted pre-established relevant information. Disagreements were resolved through consensus, and a third investigator was consulted whenever a consensus could not be achieved (NV).

2.2. Eligibility criteria

We included observational studies (cross-sectional, prospective, case-control and cohort studies) in which data on patients meeting either Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria for BD and prevalence of treatment-emergent affective switches were clearly reported. Peer-reviewed original reports

published in any language were considered for inclusion if the operational criteria for defining the affective switch were stated. Articles were excluded in the following cases: interventional studies, case reports, case series, or animal studies. In addition, we excluded studies enrolling youths (<18 years old) to an extent superior to 5% of the study population without distinguishing between adults and children/adolescents in data processing, studies not considering treatment-emergent mood switches or not providing specific data on mood switches in BD subjects, and studies focusing on switches with no antidepressant or antipsychotic drugs involved.

2.3. Data extraction and quality assessment

Using a structured spread sheet, data on the following characteristics were extracted: author, publication year, country, study design, sample size, type of switch investigated, criteria for defining affective switch, type of considered drugs, prevalence of affective switches in the considered sample, and characteristics associated with affective switches.

We appraised the quality of included case-control and cohort studies by using the Newcastle-Ottawa Quality Assessment Scale (NOS), in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; the ascertainment of either the exposure or outcome of interest. The quality of included cross sectional studies was assessed through the NOS scale adapted for cross-sectional studies (Wells et al., 2014).

Two authors (MB and GM) extracted data and assessed each included study according to the NOS criteria for cohort and cross-sectional studies. Disagreements were resolved through consensus.

2.4. Synthesis of results

Due to the anticipated heterogeneity in terms of study design, participants, and outcomes, we conducted a narrative synthesis of the available studies.

3. Results

3.1. Systematic search results

The literature search initially yielded 447 records, of which 86 were identified as duplicates. After performing the full-text review, 297 papers were excluded. Among the 64 papers that underwent full-text screening, 24 were deemed eligible for inclusion. The hand-screening of relevant references led to the further inclusion of 8 articles. Subsequently, a total of 32 papers were considered for the present systematic review. For the whole systematic search process description, see *Figure 1*.

3.2. Content results

3.2.1. General characteristics of the analyzed studies

Among the included studies, 10 were prospective studies whilst the remaining ones relied on a retrospective or cross-sectional design. Most research was conducted in outpatient settings (N = 17), with 6 studies including inpatients and 9 studies comprising both in- and out-patients. In the majority of cases, manic switches were analyzed (N = 29) while depressive switches were investigated less frequently (N = 3); none of the evaluated studies focused on both manic and depressive switches. Of the papers focusing on manic switches, 11 also included the occurrence of a mixed episode (see *Table 1 and Table 2*).

Study samples varied widely (from 28 to 3,240 subjects) and in most cases (N = 25), subjects suffering from both type I and type II BD were included. As for pharmacological treatment, 7 of the studies focusing on manic switches included subjects on AD monotherapy. In the other 22 studies, subjects taking drug combinations with mood stabilizers, antipsychotics, and benzodiazepines were also considered. None of the studies evaluating depressive switches as primary outcome included subjects receiving antipsychotics as monotherapy.

3.2.2. Hypomanic/manic switches: prevalence and clinical correlates

Among the included studies, the rate of TEM in subjects suffering from BD ranged from 17.3% to 48.8% (Benazzi, 1997; Berkol et al., 2019; Bottlender et al., 2004; Fornaro et al., 2018b; Ghaemi et al., 2004; Goldberg and Whiteside, 2002; Gorwood et al., 2016; Joffe et al., 2002; Mundo et al., 2006; Valentí et al., 2012). In the study of Undurraga et al. (2012), the use of ADs determined a 7.4 time higher risk of manic switches in depressed BD subjects. Of note, in one study, manic switch

rates were similar in two populations of BD subjects with and without AD treatment (Carlson et al., 2007).

TEM was more frequent in case of AD monotherapy (Berkol et al., 2019; Pacchiarotti et al., 2011; Viktorin et al., 2014), whilst treatment with mood stabilizers, especially lithium (Henry et al., 2001; Jann et al., 1982), or second generation antipsychotics resulted to protect against switch (Fornaro et al., 2018a; Ghaemi et al., 2004; Mundo et al., 2006; Serretti et al., 2003), although the finding was not univocal (Solomon et al., 1990; Tondo et al., 2013).

The incidence of TEM significantly differed between type I and type II BD subjects, with the exception of one study including subjects with rapid cycling BD (Gao et al., 2008). Particularly, a higher switch rate was reported in type II BD subjects in one study (Tondo et al., 2013). In a multivariable regression model, BD II was identified as an apparent predictor of TEM, despite no consensus was achieved (Benazzi, 1997). Furthermore, subjects with type II BD also demonstrated an earlier occurrence of hypomanic switches (Tondo et al., 2013).

In studies assessing subjects suffering from comorbid BD and substance-related disorders, AD monotherapy was more frequently associated with TEM, with no significant differences among type I and type II BD (Lieberman et al., 2009).

As for the type of AD more frequently associated with TEM, a higher likelihood of switching with tricyclics (Koszewska and Rybakowski, 2009; Manwani et al., 2006; Mundo et al., 2006) and a lower rate with bupropion (Joffe et al., 2002; Manwani et al., 2006) were reported. However, one retrospective study found that the switching rate was similar among different pharmacological classes (Ghaemi et al., 2004). Furthermore, the risk of TEM was higher after a shorter duration of AD treatment (Berkol et al., 2019; Koszewska and Rybakowski, 2009; Viktorin et al., 2014) and in case of previous poorer response to ADs (Valentí et al., 2012).

Females represented a more vulnerable population for manic switches than males (Koszewska and Rybakowski, 2009; Manwani et al., 2006). In addition, clinical features predicting the emergence of a manic switch in BD subjects treated with ADs were the presence of previous TEM (Gorwood et

al., 2016; Valentí et al., 2012), earlier age at onset (Valentí et al., 2012), depressive polarity of first affective episode (Koszewska and Rybakowski, 2009; Serretti et al., 2003), a history of previous hospitalizations (Fornaro et al., 2018a), and substance abuse (Goldberg and Whiteside, 2002; Manwani et al., 2006).

Continuous and rapid cycling BD courses represented other clinical characteristics associated with manic switches (Serretti et al., 2003; Tundo et al., 2015), as well as mixed features, that have been shown to accelerate the occurrence of affective switch (Bottlender et al., 2004). In one report on rapid cycling BD, subjects with a history of manic switching showed less psychotic symptoms (Serretti et al., 2003), whilst in another one, no significant associations were detected among TEM and psychosis in rapid cycling BD (Gao et al., 2008).

3.2.3 Depressive switches: prevalence and clinical correlates

According to the included studies, the reported rate of depressive switch in type I BD subjects was 5-16% (Maccariello et al., 2020; Vieta et al., 2009; Zarate et al., 2001) while no data was provided regarding the depressive switch in type II BD subjects. Depressive switches were significantly associated with the use of first-generation antipsychotic, as well as with the concomitant use of first- and second-generation antipsychotics (Maccariello et al., 2020). The use of benzodiazepines could represent an adjunctive risk factor for switching into depression (Vieta et al., 2009). Furthermore, higher number of previous depressive episodes (Vieta et al., 2009), depressive predominant polarity, and higher scores for depressive affective temperament as evaluated by tailored scales were associated with depressive switches (Maccariello et al., 2020). In a prospective study, substance abuse also represented a risk factor for switching into depression during the observation period (Vieta et al., 2009). Furthermore, a higher clinical severity as measured by the Clinical Global Impression – Bipolar Version (CGI-BP) was associated with a higher likelihood of a depressive switch (Vieta et al., 2009) and so did a higher score at the Hamilton Depression Rating Scale (Zarate et al., 2001).

3.2.4. Quality assessment of selected studies

When performing quality assessment for cohort studies by means of the Newcastle-Ottawa Scale, the selected populations appeared adequately representative in most cases and a low risk of selection biases was detected. Conversely, that were some flaws concerning comparability, as the majority of studies did not control for important factors that may influence the emergence of an affective switch. In addition, in some cases, outcome assessment was affected by insufficient reporting or subjects lost to follow-up. Among cross-sectional studies, the main quality flaws concerned sample selection and comparability, as well as the obvious limitations related to causality (Vieta and Angst, 2021). Furthermore, in some cases, outcome reporting lacked a detailed description of the statistical analysis, thus not providing sufficient information (see *Supplementary material, Table 2, and Table 3*).

4. Discussion

In the present systematic review of naturalistic studies, a high prevalence of AD-emergent mood switches in subjects suffering from BD was highlighted. On the other hand, this review confirmed the lack of investigation focusing on antipsychotic-emergent depressive switches.

On average, approximately one-third of subjects with BD experienced TEM in the included studies, with rates reaching almost 50% (Ghaemi et al., 2004). Consequently, our results confirm the need for close clinical monitoring in BD subjects prescribed with ADs in order to recognize the possible emergence of an episode of mood elevation (Fornaro et al., 2018b; Pacchiarotti et al., 2013).

The high heterogeneity in the prevalence of TEM (17-49%) may be partly attributed to the widely varying diagnostic criteria and duration of follow-ups. Indeed, according to ISBD criteria, some studies included an 8-week follow-up from the start of AD treatment or from the last change in dosage or type of AD (Ghaemi et al., 2004; Gorwood et al., 2016; Joffe et al., 2002; Valentí et al., 2012), while other studies envisaged longer observation periods (Benazzi, 1997; Berkol et al., 2019; Fornaro et al., 2018a; Goldberg and Whiteside, 2002) or did not mention specific chronological criteria to define TEM (Bottlender et al., 2004; Mundo et al., 2006). In our review, TEM was reported

to be associated with a short duration of AD treatment. This is partially in contrast with previous reports claiming relative safety of AD use for bipolar depression in the short-term (Gijsman et al., 2004; Sachs et al., 2007). Nevertheless, with a view to individualized treatment that takes into account the chronic course of BD, future prospective studies should investigate manic/hypomanic episodes associated with both short-term and long-term AD use, as well as investigate other possible clinical indicators of mood destabilization associated with AD.

TEM was more frequently associated with AD monotherapy, which is in line with current guidelines recommending caution when using this treatment strategy in BD subjects (Goodwin et al., 2016; Yatham et al., 2018).

Although many previous studies and systematic reviews have shown the opposite (Altshuler et al., 2006; Post et al., 2001), some of the studies selected in this review indicated a higher prevalence of TEM in type II BD compared to type I BD. This could be at least partially explained by the consistent prescription of ADs in subjects with type II BD, as they usually spend more time in depressive phases than in mood elevation phases (Grover et al., 2021; Weinstock et al., 2010). In addition, failure to recognize prior hypomanic phases in a depressed subject with type II BD often results in a diagnosis of major depressive disorder and, consequently, the prescription of ADs as monotherapy. In contrast, due to higher severity of mood episodes (Serafini et al., 2019) and difficulties in achieving remission (Fung et al., 2019), subjects suffering from type I BD often receive multi-pharmacological therapy with mood stabilizers or antipsychotics which could prevent, at least in part, the risk of TEM. This trend support the ISBD suggestion that mood stabilizer therapy should be considered before evaluating ADs in bipolar depression (Pacchiarotti et al., 2013). On the other hand, findings concerning mood stabilizers and antipsychotics have not been univocal in the studies considered, suggesting that risk/benefit ratios should always be evaluated in the perspective of a personalized therapeutic approach, based on psychopathological characteristics, neuroimaging findings, and biomarkers (Perugi et al., 2019). In this regard, it is noteworthy that the risk factors for treatment-emergent switches should be interpreted considering the multifactorial influence of

different mediators and moderators (Goldberg, 2019). In addition, in two of the included studies, the hypomanic/manic switch rate was similar between BD subjects with and without treatment with ADs, confirming that the risk for switching is a characteristic of BD *per se* and causality should therefore be pointed out with caution (Gitlin, 2018; Perlis et al., 2010).

When evaluating different AD classes, tricyclics were associated with higher rates of hypomanic/manic switches in most of the considered literature, confirming findings from previous reports (Gijsman et al., 2004) and corroborating the indication for avoiding these drugs and possibly preferring second-generation ADs, particularly bupropion (Goodwin et al., 2016).

According to the literature reviewed, TEM is associated with a previous history of TEM and poor response to prior AD therapies. Consequently, special attention should be paid in collecting the clinical history of BD subjects, since this could significantly help in tailoring pharmacological strategies, especially when acute treatment of bipolar depression is needed (Gitlin, 2018). In addition, rapid cycling, mixed features, substance abuse, and younger age at onset were associated with a higher risk for switching into hypomania or mania following AD treatment and thus need to be carefully assessed (Kessing and Faurholt-Jepsen, 2022; G Perugi et al., 2019). Indeed, ADs are known to be a trigger for a rapid cycling course in BD subjects (Cheniaux and Nardi, 2019; Yalin and Young, 2020). Furthermore, rapid cycling is associated with a higher prevalence of mixed features and substance abuse in BD (Furio et al., 2021), consistently with our findings. It should also be considered that the above-mentioned clinical features are also associated with higher severity and poor prognosis, suggesting that a history of TEM could represent a marker of clinical severity in BD subjects (Joslyn et al., 2016).

It is noteworthy that this is the first systematic review to investigate prevalence and clinical correlates of depressive switches in BD subjects receiving treatment for a hypomanic or manic episode. Despite wide variability across studies, depressive switches have shown a prevalence up to 15% when treating acute episodes of mania or during maintenance treatment and should therefore not be overlooked in clinical practice. Indeed, time spent in depressive phases seriously impacts overall

quality of life and functioning in BD subjects, also representing a major challenge for pharmacological treatment (Baldessarini et al., 2020). In addition, a depressive switch could worsen the long-term course of BD, as happens with hypomanic or manic switches. Data from the present review suggest that specific characteristics, such as the number of previous depressive episodes, depressive predominant polarity, and a predominant depressive affective temperament, are associated with depressive switches in BD. In particular, the predominant polarity seems to play a crucial role in the risk of depressive switch and thus represents a useful clinical marker for BD staging and characterization, helping to tailor treatment options (Colom et al., 2006; Pallaskorpi et al., 2019; Popovic et al., 2014; Rosa et al., 2008). This issue, which is emphasized in most treatment guidelines (Fountoulakis et al., 2017; Goodwin et al., 2016), has unfortunately not been included in the current classification of mental disorders (Kessing et al., 2021; Stein et al., 2020). Finally, increased clinical severity has been shown in BD subjects experiencing depressive switches.

Although many depressive switches seem to occur as a consequence of the spontaneous course of bipolar illness (Angst, 1987), they were significantly associated with the use of first-generation antipsychotics, as well as with the concomitant use of first- and second-generation antipsychotics. Given the paucity of data in the literature, the present review cannot be considered comprehensive regarding the prevalence of antipsychotic-emergent depressive switches in BD subjects. Although the association of treatment-emergent depressive switches with first generation antipsychotics has long been known (Morgan, 1972) and there are indications of a potential depressogenic effect of antipsychotics (Goikolea et al., 2013; Tohen et al., 2003a), further investigation is strongly needed.

In particular, future studies should investigate the prevalence and clinical correlates of depressive switches associated with different types of antipsychotics, focusing separately on short- and long-term use. For example, first-generation and combinations of first- and second-generation antipsychotics appear to be more depressogenic than partial agonists (e.g., aripiprazole, brexpiprazole, cariprazine) and other second-generation multi-acting receptor-targeted antipsychotics (e.g., olanzapine, quetiapine, clozapine), at least in the short term (Vieta et al., 2009). Finally, in a

substantial proportion of patients with BD, long-term treatment with any type of antipsychotic may adversely affect the course of the illness, leading to the development of negative symptoms and/or super sensitivity phenomena (Cosci and Chouinard, 2020).

Finally, it is worth noting that treatment-emergent switches are not solely associated with ADs or antipsychotics, but also with other drug classes. For example, benzodiazepines have been associated with depressive switches (Vieta et al., 2009) and few cases of lamotrigine-associated mania have been reported (Anmella et al., 2022).

In conclusion, future and more homogeneous studies of BD subjects treated pharmacologically for a depressive or hypomanic/manic episode are needed to clarify the phenotype of subjects who experience mood switches and to evaluate the specific role of different pharmacological agents. Follow-up studies should assess both manic and depressive symptoms over time, regardless of the index episode because prospectively measuring only the symptoms of the index episode does not allow the detection of affective switches and may lead to a misinterpretation of the results. Treatment of BD should always address the long-term course in BD, with particular attention to the risk of mood switches resulting from pharmacological treatment that negatively affect prognosis and treatment response.

5. Limitations

The results of the present systematic review should be interpreted in consideration of its limitations. First, there was a significant heterogeneity among the included studies in terms of setting, sample, definition, and evaluation of affective switches, which limited the possibility of comparisons. Furthermore, the included studies often had small sample sizes, with subsequent limitations in the generalizability of findings. It should also be underline that some methodological flaws where highly prevalent in the considered literature, particularly regarding control factors, sample selection, and comparability. Finally, due to the naturalistic setting in which studies were carried out, there was a high rate of polypharmacotherapy in the included research, which may have to some extent biased

the association between antidepressant and antipsychotic drugs and the emergence of manic and depressive switches. On the other hand, the strength of including only observational studies lies in their greater suitability to study BD course characteristics, including short- and long-term mood swings due to treatment. Indeed, naturalistic studies usually involve longer follow-up periods, broader sample inclusion criteria, and clinician-rated outcomes, thus reflecting clinical reality more closely than clinical trials. The latter, on the other hand, are often designed to test short-term efficacy and side effects through specific rating scales in highly selected BD populations.

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A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: the role of antidepressant and antipsychotic drugs

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Contents

Abstract

The present systematic review was aimed at critically summarizing the evidence about treatment-emergent manic/hypomanic and depressive switches during the course of bipolar disorder (BD). A systematic search of the MEDLINE, EMBASE, CINAHL, Web of Science, and PsycInfo electronic databases was conducted until March 24th, 2021, according to the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (*PRISMA*) statement. Observational studies clearly reporting data regarding the prevalence of treatment-emergent mood switches in patients with BD were considered for inclusion. Thirty-two original studies met the inclusion criteria. In the majority of cases, manic switches were analyzed; only 3 papers investigated depressive switches in type I BD. Treatment-emergent mania/hypomania in BD subjects ranged from 17.3% to 48.8% and was more frequent with antidepressant monotherapy compared to combination treatment with mood stabilizers, especially lithium, or second-generation antipsychotics. A higher likelihood of mood switch has been reported with tricyclics and a lower rate with bupropion. Depressive switches were detected in 5-16% of type I BD subjects and were associated with first-generation antipsychotic use, the concomitant use of first- and second-generation antipsychotics, and benzodiazepines. The included studies presented considerable methodological heterogeneity, small sample sizes and comparability flaws. In conclusion, many studies, although heterogeneous and partly discordant, have been conducted on manic/hypomanic switches, whereas depressive switches during treatment with antipsychotics are poorly investigated. In BD subjects, both antidepressant and antipsychotic medications seems to play a role in the occurrence of mood switches, although the effects of different pharmacological compounds have yet to be fully investigated.

Keywords

Bipolar Disorder; mood switch; treatment-emergent mania; treatment-emergent depression.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating psychiatric illness characterized by recurrent depressive, hypomanic/manic, and mixed episodes (Vieta et al., 2018). Mood switch, i.e., the abrupt transition from one mood episode to another episode of opposite polarity, has long been known as a core feature of BD (Salvadore et al., 2010). With the advent of modern psychopharmacology, treatment-emergent affective switches have become an increasingly relevant clinical issue. Recently, guidelines for bipolar treatment from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) have highlighted the risk of treatment-induced manic and depressive switches in individuals with BD (Yatham et al., 2018). Indeed, antidepressants (ADs), and especially tricyclics, could trigger a hypomanic/manic or mixed episode in depressed subjects suffering from BD (Koszewska and Rybakowski, 2009; Leverich et al., 2006). On the other hand, first-generation antipsychotics might be associated with depressive switches in individuals treated for a manic or mixed episode, whereas there are still contrasting data on the risk of switches with second-generation antipsychotics (Goikolea et al., 2013; Tohen et al., 2003a).

The AD-associated transition from depression to mania has been a widely studied topic over the years. The ISBD task force defines treatment-emergent mania or hypomania (TEM) as a full syndromic hypomanic, manic, or mixed episode that lasts at least 2 consecutive days and occurs up to 8 weeks after the putative causal intervention (last treatment change) (Tohen et al., 2009). The task force recommends further consideration of including the specific treatment (i.e., AD-associated switch) if the switch emerges within less than 2 weeks. However, operational definitions of TEM and methodological assessments widely varied across studies, leading to inconsistent findings regarding the prevalence of TEM and its clinical risk factors. A recent systematic review reported a TEM prevalence of 31% in BD subjects (Fornaro et al., 2018b). However, the authors highlighted the need for more homogeneous studies that should investigate both short- and long-term affective switches.

Despite the lack of widespread agreement on the possible role of several ADs in triggering mood switches, these medications are recommended in association with a mood stabilizing therapy in depressed subjects suffering from BD, particularly those with type I BD (Pacchiarotti et al., 2013; Viktorin et al., 2014). In fact, aside from TEM, AD treatment has been associated with mixed features, dysphoria, irritability, rapid cycling, and increased suicide risk (El-Mallakh et al., 2008; Lee et al., 2013).

On the other hand, the switch from mania to depression has often been neglected by both the clinical and the research community. Indeed, few studies have explored its prevalence, as well as possible clinical and pharmacological factors associated with this particular phenomenon (Goikolea et al., 2013; Vieta et al., 2009). A depressive switch has been estimated in 13% of BD subjects at their first manic episode (Tohen et al., 2003b) and antipsychotics, mainly typical ones, seem to play a role in increasing this risk (Tohen et al., 2003a; Zarate and Tohen, 2004). Treatment-emergent depressive switch is defined as a full syndromic depressive episodes lasting at least 1 week and occurring up to 8 weeks from the last change in treatment (Tohen et al., 2009). As for TEM, the ISBD task force recommends referring to an antipsychotic-associated switch if it occurs within less than 2 weeks of starting treatment. As for acute bipolar depression, pharmacological treatment of acute mania and mixed states needs to be chosen carefully in order to reduce the risk of a depressive switch (Vieta, 2005).

Based on these premises, the primary objective of the present systematic review is to assess the prevalence of treatment-emergent mood switches in samples of subjects with BD evaluated in a naturalistic setting. A second objective is to investigate the possible clinical correlates that distinguish BD subjects with treatment-emergent switches from those not presenting this condition. In our opinion, the context of naturalistic, observational studies is best suited to investigate treatment-emergent episodes and the one that most reflects routine clinical practice, involving BD subjects with chronic and highly cyclical course, multiple comorbidities, and drug combinations. In addition, observational studies focus primarily on physician-assessed course characteristics and global

functioning. In contrast, interventional trials usually involve highly selected subjects, short follow-up periods, and rely mainly on rating scales designed to test for short-term efficacy and side effects.

2. Methods

This review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009; Page et al., 2021). Search methods and results are highlighted in Figure 1. A study protocol was registered with PROSPERO and published a priori (CRD42021233638).

2.1. Search strategy

First, a comprehensive computerized literature search of five bibliographical databases – MEDLINE, EMBASE, CINAHL, Web of Science, and PsycInfo – was performed from inception to March 24th, 2021, cross-checking the obtained references. Detailed search strings are provided in the *Supplementary material S1* that accompanies the online edition of this article. Secondly, we conducted a manual search of the reference lists of included articles to supplement the electronic searches (see references of studies excluded after full-text review and reasons for exclusions in the *Supplementary material*, *Table 1*).

Two independent investigators (MB and GM) screened title/abstracts of retrieved references for eligibility, evaluated the full texts of potentially eligible articles, and extracted pre-established relevant information. Disagreements were resolved through consensus, and a third investigator was consulted whenever a consensus could not be achieved (NV).

2.2. Eligibility criteria

We included observational studies (cross-sectional, prospective, case-control and cohort studies) in which data on patients meeting either Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria for BD and prevalence of treatment-emergent affective switches were clearly reported. Peer-reviewed original reports

published in any language were considered for inclusion if the operational criteria for defining the affective switch were stated. Articles were excluded in the following cases: interventional studies, case reports, case series, or animal studies. In addition, we excluded studies enrolling youths (<18 years old) to an extent superior to 5% of the study population without distinguishing between adults and children/adolescents in data processing, studies not considering treatment-emergent mood switches or not providing specific data on mood switches in BD subjects, and studies focusing on switches with no antidepressant or antipsychotic drugs involved.

2.3. Data extraction and quality assessment

Using a structured spread sheet, data on the following characteristics were extracted: author, publication year, country, study design, sample size, type of switch investigated, criteria for defining affective switch, type of considered drugs, prevalence of affective switches in the considered sample, and characteristics associated with affective switches.

We appraised the quality of included case-control and cohort studies by using the Newcastle-Ottawa Quality Assessment Scale (NOS), in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; the ascertainment of either the exposure or outcome of interest. The quality of included cross sectional studies was assessed through the NOS scale adapted for cross-sectional studies (Wells et al., 2014).

Two authors (MB and GM) extracted data and assessed each included study according to the NOS criteria for cohort and cross-sectional studies. Disagreements were resolved through consensus.

2.4. Synthesis of results

Due to the anticipated heterogeneity in terms of study design, participants, and outcomes, we conducted a narrative synthesis of the available studies.

3. Results

3.1. Systematic search results

The literature search initially yielded 447 records, of which 86 were identified as duplicates. After performing the full-text review, 297 papers were excluded. Among the 64 papers that underwent full-text screening, 24 were deemed eligible for inclusion. The hand-screening of relevant references led to the further inclusion of 8 articles. Subsequently, a total of 32 papers were considered for the present systematic review. For the whole systematic search process description, see *Figure 1*.

3.2. Content results

3.2.1. General characteristics of the analyzed studies

Among the included studies, 10 were prospective studies whilst the remaining ones relied on a retrospective or cross-sectional design. Most research was conducted in outpatient settings (N = 17), with 6 studies including inpatients and 9 studies comprising both in- and out-patients. In the majority of cases, manic switches were analyzed (N = 29) while depressive switches were investigated less frequently (N = 3); none of the evaluated studies focused on both manic and depressive switches. Of the papers focusing on manic switches, 11 also included the occurrence of a mixed episode (see *Table 1 and Table 2*).

Study samples varied widely (from 28 to 3,240 subjects) and in most cases (N = 25), subjects suffering from both type I and type II BD were included. As for pharmacological treatment, 7 of the studies focusing on manic switches included subjects on AD monotherapy. In the other 22 studies, subjects taking drug combinations with mood stabilizers, antipsychotics, and benzodiazepines were also considered. None of the studies evaluating depressive switches as primary outcome included subjects receiving antipsychotics as monotherapy.

3.2.2. Hypomanic/manic switches: prevalence and clinical correlates

Among the included studies, the rate of TEM in subjects suffering from BD ranged from 17.3% to 48.8% (Benazzi, 1997; Berkol et al., 2019; Bottlender et al., 2004; Fornaro et al., 2018b; Ghaemi et al., 2004; Goldberg and Whiteside, 2002; Gorwood et al., 2016; Joffe et al., 2002; Mundo et al., 2006; Valentí et al., 2012). In the study of Undurraga et al. (2012), the use of ADs determined a 7.4 time higher risk of manic switches in depressed BD subjects. Of note, in one study, manic switch

rates were similar in two populations of BD subjects with and without AD treatment (Carlson et al., 2007).

TEM was more frequent in case of AD monotherapy (Berkol et al., 2019; Pacchiarotti et al., 2011; Viktorin et al., 2014), whilst treatment with mood stabilizers, especially lithium (Henry et al., 2001; Jann et al., 1982), or second generation antipsychotics resulted to protect against switch (Fornaro et al., 2018a; Ghaemi et al., 2004; Mundo et al., 2006; Serretti et al., 2003), although the finding was not univocal (Solomon et al., 1990; Tondo et al., 2013).

The incidence of TEM significantly differed between type I and type II BD subjects, with the exception of one study including subjects with rapid cycling BD (Gao et al., 2008). Particularly, a higher switch rate was reported in type II BD subjects in one study (Tondo et al., 2013). In a multivariable regression model, BD II was identified as an apparent predictor of TEM, despite no consensus was achieved (Benazzi, 1997). Furthermore, subjects with type II BD also demonstrated an earlier occurrence of hypomanic switches (Tondo et al., 2013).

In studies assessing subjects suffering from comorbid BD and substance-related disorders, AD monotherapy was more frequently associated with TEM, with no significant differences among type I and type II BD (Lieberman et al., 2009).

As for the type of AD more frequently associated with TEM, a higher likelihood of switching with tricyclics (Koszewska and Rybakowski, 2009; Manwani et al., 2006; Mundo et al., 2006) and a lower rate with bupropion (Joffe et al., 2002; Manwani et al., 2006) were reported. However, one retrospective study found that the switching rate was similar among different pharmacological classes (Ghaemi et al., 2004). Furthermore, the risk of TEM was higher after a shorter duration of AD treatment (Berkol et al., 2019; Koszewska and Rybakowski, 2009; Viktorin et al., 2014) and in case of previous poorer response to ADs (Valentí et al., 2012).

Females represented a more vulnerable population for manic switches than males (Koszewska and Rybakowski, 2009; Manwani et al., 2006). In addition, clinical features predicting the emergence of a manic switch in BD subjects treated with ADs were the presence of previous TEM (Gorwood et

al., 2016; Valentí et al., 2012), earlier age at onset (Valentí et al., 2012), depressive polarity of first affective episode (Koszewska and Rybakowski, 2009; Serretti et al., 2003), a history of previous hospitalizations (Fornaro et al., 2018a), and substance abuse (Goldberg and Whiteside, 2002; Manwani et al., 2006).

Continuous and rapid cycling BD courses represented other clinical characteristics associated with manic switches (Serretti et al., 2003; Tundo et al., 2015), as well as mixed features, that have been shown to accelerate the occurrence of affective switch (Bottlender et al., 2004). In one report on rapid cycling BD, subjects with a history of manic switching showed less psychotic symptoms (Serretti et al., 2003), whilst in another one, no significant associations were detected among TEM and psychosis in rapid cycling BD (Gao et al., 2008).

3.2.3 Depressive switches: prevalence and clinical correlates

According to the included studies, the reported rate of depressive switch in type I BD subjects was 5-16% (Maccariello et al., 2020; Vieta et al., 2009; Zarate et al., 2001) while no data was provided regarding the depressive switch in type II BD subjects. Depressive switches were significantly associated with the use of first-generation antipsychotic, as well as with the concomitant use of first- and second-generation antipsychotics (Maccariello et al., 2020). The use of benzodiazepines could represent an adjunctive risk factor for switching into depression (Vieta et al., 2009). Furthermore, higher number of previous depressive episodes (Vieta et al., 2009), depressive predominant polarity, and higher scores for depressive affective temperament as evaluated by tailored scales were associated with depressive switches (Maccariello et al., 2020). In a prospective study, substance abuse also represented a risk factor for switching into depression during the observation period (Vieta et al., 2009). Furthermore, a higher clinical severity as measured by the Clinical Global Impression – Bipolar Version (CGI-BP) was associated with a higher likelihood of a depressive switch (Vieta et al., 2009) and so did a higher score at the Hamilton Depression Rating Scale (Zarate et al., 2001).

3.2.4. Quality assessment of selected studies

When performing quality assessment for cohort studies by means of the Newcastle-Ottawa Scale, the selected populations appeared adequately representative in most cases and a low risk of selection biases was detected. Conversely, that were some flaws concerning comparability, as the majority of studies did not control for important factors that may influence the emergence of an affective switch. In addition, in some cases, outcome assessment was affected by insufficient reporting or subjects lost to follow-up. Among cross-sectional studies, the main quality flaws concerned sample selection and comparability, as well as the obvious limitations related to causality (Vieta and Angst, 2021). Furthermore, in some cases, outcome reporting lacked a detailed description of the statistical analysis, thus not providing sufficient information (see *Supplementary material, Table 2, and Table 3*).

4. Discussion

In the present systematic review of naturalistic studies, a high prevalence of AD-emergent mood switches in subjects suffering from BD was highlighted. On the other hand, this review confirmed the lack of investigation focusing on antipsychotic-emergent depressive switches.

On average, approximately one-third of subjects with BD experienced TEM in the included studies, with rates reaching almost 50% (Ghaemi et al., 2004). Consequently, our results confirm the need for close clinical monitoring in BD subjects prescribed with ADs in order to recognize the possible emergence of an episode of mood elevation (Fornaro et al., 2018b; Pacchiarotti et al., 2013).

The high heterogeneity in the prevalence of TEM (17-49%) may be partly attributed to the widely varying diagnostic criteria and duration of follow-ups. Indeed, according to ISBD criteria, some studies included an 8-week follow-up from the start of AD treatment or from the last change in dosage or type of AD (Ghaemi et al., 2004; Gorwood et al., 2016; Joffe et al., 2002; Valentí et al., 2012), while other studies envisaged longer observation periods (Benazzi, 1997; Berkol et al., 2019; Fornaro et al., 2018a; Goldberg and Whiteside, 2002) or did not mention specific chronological criteria to define TEM (Bottlender et al., 2004; Mundo et al., 2006). In our review, TEM was reported

to be associated with a short duration of AD treatment. This is partially in contrast with previous reports claiming relative safety of AD use for bipolar depression in the short-term (Gijsman et al., 2004; Sachs et al., 2007). Nevertheless, with a view to individualized treatment that takes into account the chronic course of BD, future prospective studies should investigate manic/hypomanic episodes associated with both short-term and long-term AD use, as well as investigate other possible clinical indicators of mood destabilization associated with AD.

TEM was more frequently associated with AD monotherapy, which is in line with current guidelines recommending caution when using this treatment strategy in BD subjects (Goodwin et al., 2016; Yatham et al., 2018).

Although many previous studies and systematic reviews have shown the opposite (Altshuler et al., 2006; Post et al., 2001), some of the studies selected in this review indicated a higher prevalence of TEM in type II BD compared to type I BD. This could be at least partially explained by the consistent prescription of ADs in subjects with type II BD, as they usually spend more time in depressive phases than in mood elevation phases (Grover et al., 2021; Weinstock et al., 2010). In addition, failure to recognize prior hypomanic phases in a depressed subject with type II BD often results in a diagnosis of major depressive disorder and, consequently, the prescription of ADs as monotherapy. In contrast, due to higher severity of mood episodes (Serafini et al., 2019) and difficulties in achieving remission (Fung et al., 2019), subjects suffering from type I BD often receive multi-pharmacological therapy with mood stabilizers or antipsychotics which could prevent, at least in part, the risk of TEM. This trend support the ISBD suggestion that mood stabilizer therapy should be considered before evaluating ADs in bipolar depression (Pacchiarotti et al., 2013). On the other hand, findings concerning mood stabilizers and antipsychotics have not been univocal in the studies considered, suggesting that risk/benefit ratios should always be evaluated in the perspective of a personalized therapeutic approach, based on psychopathological characteristics, neuroimaging findings, and biomarkers (Perugi et al., 2019). In this regard, it is noteworthy that the risk factors for treatment-emergent switches should be interpreted considering the multifactorial influence of

different mediators and moderators (Goldberg, 2019). In addition, in two of the included studies, the hypomanic/manic switch rate was similar between BD subjects with and without treatment with ADs, confirming that the risk for switching is a characteristic of BD *per se* and causality should therefore be pointed out with caution (Gitlin, 2018; Perlis et al., 2010).

When evaluating different AD classes, tricyclics were associated with higher rates of hypomanic/manic switches in most of the considered literature, confirming findings from previous reports (Gijsman et al., 2004) and corroborating the indication for avoiding these drugs and possibly preferring second-generation ADs, particularly bupropion (Goodwin et al., 2016).

According to the literature reviewed, TEM is associated with a previous history of TEM and poor response to prior AD therapies. Consequently, special attention should be paid in collecting the clinical history of BD subjects, since this could significantly help in tailoring pharmacological strategies, especially when acute treatment of bipolar depression is needed (Gitlin, 2018). In addition, rapid cycling, mixed features, substance abuse, and younger age at onset were associated with a higher risk for switching into hypomania or mania following AD treatment and thus need to be carefully assessed (Kessing and Faurholt-Jepsen, 2022; G Perugi et al., 2019). Indeed, ADs are known to be a trigger for a rapid cycling course in BD subjects (Cheniaux and Nardi, 2019; Yalin and Young, 2020). Furthermore, rapid cycling is associated with a higher prevalence of mixed features and substance abuse in BD (Furio et al., 2021), consistently with our findings. It should also be considered that the above-mentioned clinical features are also associated with higher severity and poor prognosis, suggesting that a history of TEM could represent a marker of clinical severity in BD subjects (Joslyn et al., 2016).

~~Finally, it should be emphasized that TEM also occurs in individuals with major depressive disorders, albeit at a lower frequency than BD, and may represent a marker of bipolarity in this population. In fact, previous literature identifies several predictors of unrecognized BD in major depressive subjects with TEM. (Angst et al., 2012; Barbuti et al., 2017). Subsequently, attention should be paid to AD monotherapy in subjects with a major depressive episode who display high-risk~~

~~factors for developing BD, e.g., a positive family history for BD (Scott et al., 2017; Yatham et al., 2018) or the presence of mixed features (Perugi et al., 2015). Moreover, longitudinal observation is also required when prescribing ADs to subjects suffering from a depressive episode, since the emergence of TEM would significantly change the diagnostic framework and influence subsequent treatment strategies (Terao, 2021).~~

It is noteworthy that this is the first systematic review to investigate prevalence and clinical correlates of depressive switches in BD subjects receiving treatment for a hypomanic or manic episode. Despite wide variability across studies, depressive switches have shown a prevalence up to 15% when treating acute episodes of mania or during maintenance treatment and should therefore not be overlooked in clinical practice. Indeed, time spent in depressive phases seriously impacts overall quality of life and functioning in BD subjects, also representing a major challenge for pharmacological treatment (Baldessarini et al., 2020). In addition, a depressive switch could worsen the long-term course of BD, as happens with hypomanic or manic switches. Data from the present review suggest that specific characteristics, such as the number of previous depressive episodes, depressive predominant polarity, and a predominant depressive affective temperament, are associated with depressive switches in BD. In particular, the predominant polarity seems to play a crucial role in the risk of depressive switch and thus represents a useful clinical marker for BD staging and characterization, helping to tailor treatment options (Colom et al., 2006; Pallaskorpi et al., 2019; Popovic et al., 2014; Rosa et al., 2008). This issue, which is emphasized in most treatment guidelines (Fountoulakis et al., 2017; Goodwin et al., 2016), has unfortunately not been included in the current classification of mental disorders (Kessing et al., 2021; Stein et al., 2020). Finally, increased clinical severity has been shown in BD subjects experiencing depressive switches.

Although many depressive switches seem to occur as a consequence of the spontaneous course of bipolar illness (Angst, 1987), they were significantly associated with the use of first-generation antipsychotics, as well as with the concomitant use of first- and second-generation antipsychotics. Given the paucity of data in the literature, the present review cannot be considered comprehensive

regarding the prevalence of antipsychotic-emergent depressive switches in BD subjects. Although the association of treatment-emergent depressive switches with first generation antipsychotics has long been known (Morgan, 1972) and there are indications of a potential depressogenic effect of antipsychotics (Goikolea et al., 2013; Tohen et al., 2003a), further investigation is strongly needed.

In particular, future studies should investigate the prevalence and clinical correlates of depressive switches associated with different types of antipsychotics, focusing separately on short- and long-term use. For example, first-generation and combinations of first- and second-generation antipsychotics appear to be more depressogenic than partial agonists (e.g., aripiprazole, brexpiprazole, cariprazine) and other second-generation multi-acting receptor-targeted antipsychotics (e.g., olanzapine, quetiapine, clozapine), at least in the short term (Vieta et al., 2009). Finally, in a substantial proportion of patients with BD, long-term treatment with any type of antipsychotic may adversely affect the course of the illness, leading to the development of negative symptoms and/or super sensitivity phenomena (Cosci and Chouinard, 2020).

Finally, it is worth noting that treatment-emergent switches are not solely associated with ADs or antipsychotics, but also with other drug classes. For example, benzodiazepines have been associated with depressive switches (Vieta et al., 2009) and few cases of lamotrigine-associated mania have been reported (Anmella et al., 2022).

In conclusion, future and more homogeneous studies of BD subjects treated pharmacologically for a depressive or hypomanic/manic episode are needed to clarify the phenotype of subjects who experience mood switches and to evaluate the specific role of different pharmacological agents. Follow-up studies should assess both manic and depressive symptoms over time, regardless of the index episode because prospectively measuring only the symptoms of the index episode does not allow the detection of affective switches and may lead to a misinterpretation of the results. Treatment of BD should always address the long-term course in BD, with particular attention to the risk of mood switches resulting from pharmacological treatment that negatively affect prognosis and treatment response.

5. Limitations

The results of the present systematic review should be interpreted in consideration of its limitations. First, there was a significant heterogeneity among the included studies in terms of setting, sample, definition, and evaluation of affective switches, which limited the possibility of comparisons. Furthermore, the included studies often had small sample sizes, with subsequent limitations in the generalizability of findings. It should also be underline that some methodological flaws where highly prevalent in the considered literature, particularly regarding control factors, sample selection, and comparability. Finally, due to the naturalistic setting in which studies were carried out, there was a high rate of polypharmacotherapy in the included research, which may have to some extent biased the association between antidepressant and antipsychotic drugs and the emergence of manic and depressive switches. On the other hand, the strength of including only observational studies lies in their greater suitability to study BD course characteristics, including short- and long-term mood swings due to treatment. Indeed, naturalistic studies usually involve longer follow-up periods, broader sample inclusion criteria, and clinician-rated outcomes, thus reflecting clinical reality more closely than clinical trials. The latter, on the other hand, are often designed to test short-term efficacy and side effects through specific rating scales in highly selected BD populations.

6. References

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Table 1: summary of the studies included evaluating treatment-induced hypomanic/manic switches.

Author, year	Setting	Design	Type of switch	Switch criteria	Pharmacological agents	Sample size
Berkol, 2019	Outpatient	Retrospective chart review	Manic, hypomanic	Mood chart (graphical representation of mood fluctuations over time)	Antidepressants (SSRI, TCA, venlafaxine, mirtazapine), both monotherapy and combination with mood stabilizers and/or antipsychotics	221 BD-I euthymic subjects 17 BD-II euthymic subjects
Fornaro, 2018	Outpatient	Cross-sectional	Manic, hypomanic, mixed	ISBD task force definition	Antidepressants, possible association with mood stabilizers and/or SGA	91 BD-II depressed subjects
Takaesu, 2017	Outpatient	Cross-sectional	Manic, hypomanic	Medication-induced bipolar and related disorders according to DSM-5 criteria	Antidepressants (not specified whereas other drugs were prescribed)	41 BD-I euthymic subjects 63 BD-II euthymic subjects ~~73 MDD euthymic subjects~~
Barbuti, 2017	Inpatient and outpatient	Cross-sectional	Manic, hypomanic	DSM-IV-TR criteria	Antidepressants, possible association with mood stabilizers and/or antipsychotics	464 BD depressed subjects ~~1872 MDD depressed subjects~~
Gorwood, 2016	Outpatient	Prospective (1 month)	Manic, hypomanic, mixed	Hypomanic, manic, or mixed episode (according to MINI 5.0) lasting at least two consecutive days with daily occurrence of symptomatic periods lasting more than 50% of time each day and starting within 8 weeks after start (or change) of treatment	Antidepressants (SSRI, SNRI, TCA, RIMA, atypical), mood stabilizers, possible association with antipsychotics	971 BD-I depressed subjects 271 BD-II depressed subjects
Tundo, 2015	Outpatient	Retrospective chart review	Manic, hypomanic, mixed	ISBD task force definition	Antidepressants (SSRI, SNRI, TCA), mood stabilizers, SGA	49 BD-I depressed subjects 52 BD-II depressed subjects
Viktorin, 2014	Inpatient and outpatient	Retrospective (National Registry)	Manic	ICD criteria	Antidepressants (SSRI, SNRI, TCA, bupropion), both monotherapy and combination with mood stabilizers	3240 BD subjects
Tondo, 2013	Outpatient	Retrospective chart review	Manic, hypomanic, mixed	Clinically identified through semi-structured interviews according to the mood disorder components of SCID-I	Antidepressants (SSRI, SNRI, TCA, MAOI), possible association with mood stabilizers and/or antipsychotics	93 BD-I depressed subjects 117 BD-II depressed subjects ~~668 MDD depressed subjects~~
Undurraga, 2012	Outpatient	Prospective (6 months)	Manic, hypomanic, mixed	New-onset of DSM-IV hypomania, mania, or mixed episode following initial remission	Antidepressants, mood stabilizers, antipsychotics	205 BD-I depressed subjects 85 BD-II depressed subjects
Valentì, 2012	Outpatient	Prospective (8 weeks)	Manic, mixed	ISBD task force definition	Antidepressants, mood stabilizers and/or SGA	221 BD depressed subjects

Dumlu, 2011	Inpatient and outpatient	Cross-sectional	Manic	Full DSM-IV manic episode criteria within the first 8 weeks of antidepressant treatment, ECT initiation or antidepressant augmentation	Antidepressants (TCA, SSRI, SNRI), SGA	58 BD-I subjects 17 BD-II subjects ~~141 MDD subjects~~
Pacchiarotti, 2011	Inpatient and outpatient	Retrospective and prospective (10 years)	Manic, mixed	ISBD task force definition	Antidepressants (TCA, SSRI, SNRI, bupropion), both monotherapy and combination with mood stabilizers	69 BD-I subjects 26 BD-II subjects
Lieberman, 2009	Outpatient	Cross-sectional	Manic, hypomanic, mixed	Manic, hypomanic or mixed episodes occurring within 8 weeks from antidepressant treatment	Antidepressants, mood stabilizers, SGA	18 BD-I subjects 23 BD-II subjects with comorbid SUD
Koszewska, 2009	Inpatient	Retrospective chart review	Manic, hypomanic	Direct change (without a remission period) of a depressive episode into a manic (or hypomanic) one meeting DSM-IV criteria and lasting at least 4 weeks	Antidepressants (TCA, SSRI, MAOI), possible association with mood stabilizers	333 BD depressed subjects
Bottlender, 2004	Inpatient	Retrospective chart review	Manic, hypomanic	1. Direct mood switch from the depressive state 2. DSM-IV criteria for hypomania or mania 3. The state forced clinicians to consider a change of medication or required careful watching by nurses all day long	TCA, possible association with mood stabilizers	158 BD-I depressed subjects
Ghaemi, 2004	Outpatient	Retrospective chart review and clinical interviews	Manic, hypomanic, mixed	A new DSM-IV manic, hypomanic, or mixed episode less than 8 weeks after initiation of antidepressant treatment	Antidepressants (venlafaxine, bupropion, TCA), mood-stabilizers, other "miscellaneous agents"	26 BD-I depressed subjects 10 BD-II depressed subjects 5 BD-NOS depressed subjects ~~37 MDD depressed subjects~~
Serretti, 2003	Inpatient	Retrospective chart review	Manic, hypomanic	One manic or hypomanic episode (according to DSM-IV criteria) immediately following depression without any interposed euthymic period (''switch'') during antidepressant therapy	Antidepressants (fluvoxamine, paroxetine, citalopram, other SSRI, TCA, and MAOI), mood stabilizers	96 BD-I, 73 BD-II subjects with previous antidepressant-induced switches 201 BD-I, 46 BD-II ethnicity-matched subjects without previous antidepressant - induced switches
Gitlin, 2003	Outpatient	Retrospective chart review	Manic, hypomanic	Manic or hypomanic episodes within 2 months following the depressive episode	Antidepressants (TCA, MAOI), mood stabilizers	28 BD-I depressed subjects
Henry, 2001	Inpatient and outpatient	Prospective (at least 6 weeks)	Manic, hypomanic	1. Hypomanic/manic episode according to DSM-IV criteria; 2. Follow-up of at least 6 weeks after the beginning of AD treatment; 3. A direct switch from depression to mania/hypomania with no remission prior to switching	SSRI, mood stabilizers, ECT	31 BD-I depressed subjects 13 BD-II depressed subjects

Benazzi, 1997	Outpatient	Prospective (3 to 6 months)	Manic, hypomanic	DSM-IV criteria	SSRI, TCA, SSRI+TCA	8 BD-I depressed subjects 92 BD-II depressed subjects ~~103 MDD depressed subjects~~
Solomon, 1990	Inpatient and outpatient	Retrospective chart review	Manic	DSM-III criteria for possible switch into mania while in hospital	Antidepressants (TCA, trazodone, MAOI), possible combination with lithium	33 BD depressed subjects
Carlson, 2007	Inpatient and outpatient	Prospective (4 years)	Manic, hypomanic, mixed	Manic/hypomanic/mixed episode lasting at least a week, immediately following an episode of depression, during antidepressant treatment or within 30 days of stopping the medication	Antidepressants (TCA, MAOI, SSRI, bupropion, venlafaxine, nefazodone) in combination with mood-stabilizers and/or antipsychotics	76 BD depressed subjects with psychotic features
Mundo, 2006	Outpatient	Retrospective chart review	Manic, hypomanic	Manic or hypomanic episode according to DSM-IV criteria during antidepressant treatment	Antidepressants (TCA, SSRI, NaSSA, NRI, venlafaxine, amisulpride), mood stabilizers	30 BD-I, BD-II or Schizoaffective Disorder subjects with previous antidepressant-induced switches 106 BD-I, BD-II or Schizoaffective Disorder subjects without previous antidepressant -induced switches
Stoll, 1994	Inpatient	Blind retrospective chart review	Manic, mixed	Hospital admission with the DSM-III-R diagnosis of bipolar disorder (manic or mixed phase) or schizoaffective disorder, bipolar type (manic phase) and antidepressant treatment within 2 weeks of admission	Antidepressants (TCA, fluoxetine, MAOI, bupropion), possible association with lithium and/or antipsychotics	49 BD-I manic or mixed subjects
Goldberg, 2002	Outpatient	Retrospective chart review	Manic, hypomanic	Consensus-rated manic or hypomanic symptom constellations according to DSM-IV criteria for the 12-week period after starting antidepressant	Antidepressants (SSRI, TCA, bupropion), possible association with mood stabilizers	33 BD-I subjects 18 BD-II subjects 2 BD-NOS subjects
Manwani, 2006	Inpatient	Retrospective chart review	Manic, hypomanic	A manic or hypomanic episode within 12 weeks of beginning an antidepressant trial	Antidepressants (bupropion, SSRI, TCA, other), possible association with mood stabilizers and/or antipsychotics	98 BD subjects
Gao, 2008	Outpatient	Cross-sectional	Manic, hypomanic	DSM-IV criteria	Second generation antidepressant monotherapy	99 BD-I subjects 45 BD-II subjects with rapid cycling course
Jann, 1982	Outpatient	Retrospective chart review	Manic, hypomanic	Presence of elation or irritability and a definable onset of mood disturbance, according to DSM-III criteria	TCA (imipramine, amitriptyline), lithium	30 BD subjects
Joffe, 2002	Outpatient	Prospective study (at least 1 year)	Manic	A manic episode within 8 weeks of the initiation of antidepressant therapy	SSRI, bupropion	51 BD-I subjects 18 BD-II subjects

Abbreviations. BD, Bipolar Disorder; BD-NOS, Bipolar disorder Not Otherwise Specified; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, Electroconvulsive Therapy; ICD, International Classification of Diseases; ISBD, International Society for Bipolar Disorders; MAOI, Monoamine Oxidase Inhibitor; ~~MDD, Major Depressive Disorder;~~ MINI, Mini-International Neuropsychiatric Interview; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; NRI, Norepinephrine Reuptake Inhibitor; RIMA, Reversible Inhibitor of MAO-A; SCID, Structured Clinical Interview for DSM; SGA, Second Generation Antipsychotic; SNRI, Serotonin–noradrenaline reuptake inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; SUD, Substance Use Disorder; TCA, Tricyclic Antidepressant.

Table 2: summary of the studies included evaluating treatment-induced depressive switches.

Author, year	Setting	Design	Switch criteria	Pharmacological agents	Sample size
Maccariello, 2020	Inpatient and outpatient	Prospective (12 weeks)	MADRS total score ≥ 15 and YMRS < 10	SGA (aripiprazole, asenapine, olanzapine, quetiapine, risperidone, others), FGA (haloperidol, chlorpromazine, clotiapine, others), mood stabilizers (lithium, valproate)	234 BD-I manic subjects
Vieta, 2009	Inpatient and outpatient	Prospective study (12 weeks)	CGI-BP mania score of <3 and CGI-BP depression score of ≥ 3 when, in the previous visit, the two scores were ≥ 3 and < 3, respectively	SGA, FGA, mood stabilizers (lithium, anticonvulsants), antidepressant	2390 BD-I manic or mixed subjects
Zarate, 2001	Inpatient	Prospective study (24 months)	A major depressive episode according to DSM-IV criteria immediately after a manic episode without first achieving syndromic recovery (defined as 8 weeks of euthymia).	Antipsychotics, mood-stabilizers, anxiolytics, antidepressants	28 BD-I manic subjects with a depressive switch 148 BD-I manic subjects without a depressive switch

Abbreviations. BD, Bipolar Disorder; CGI-BP, Clinical Global Impressions – Bipolar version; DSM, Diagnostic and Statistical Manual of Mental Disorders; FGA, First Generation Antipsychotic; MDRS, Montgomery Asberg Depression Rating Scale; SGA, Second Generation Antipsychotic; YMRS, Young Mania Rating Scale.

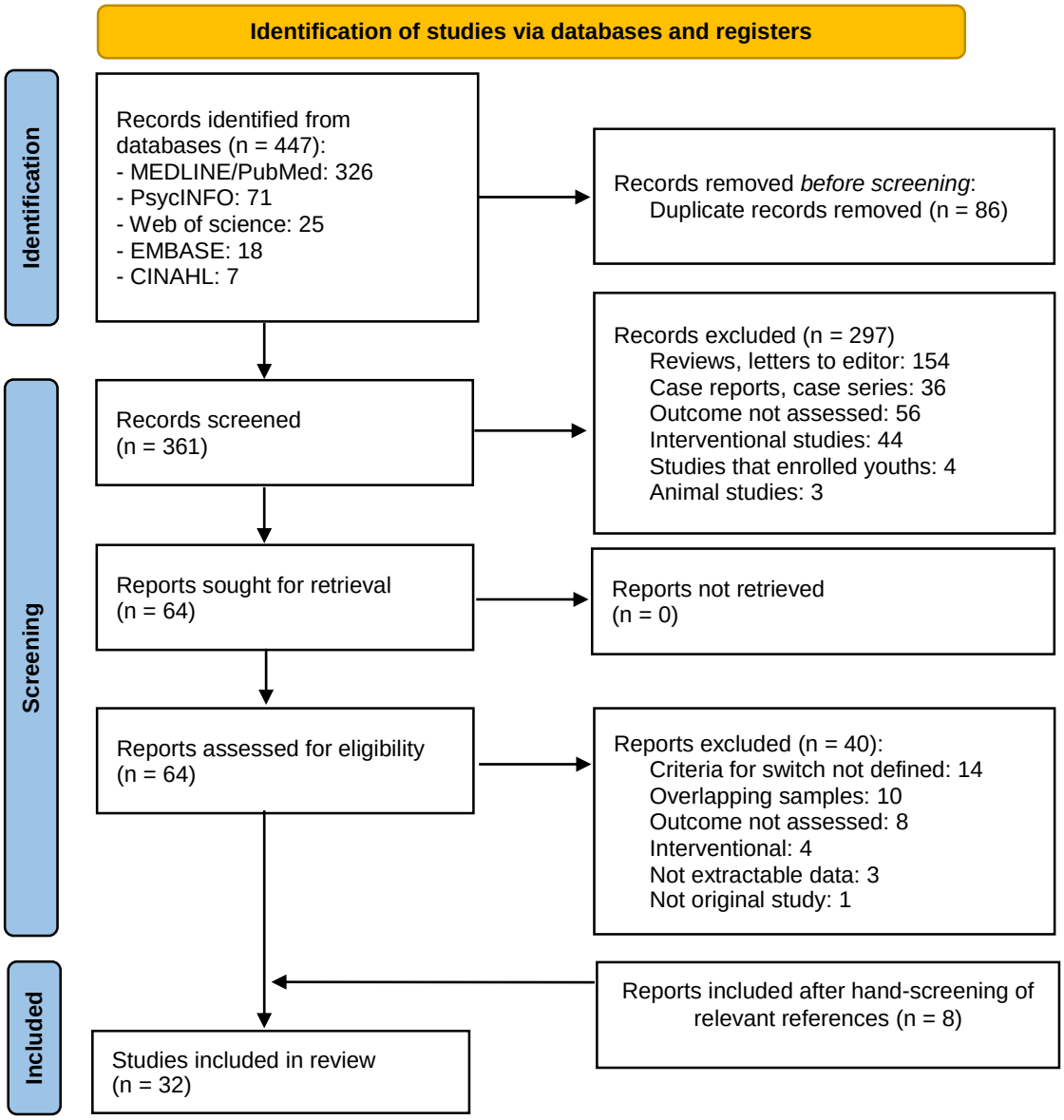

Figure 1. PRISMA 2020 flow diagram. From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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GP designed and supervised the study. MB and GM wrote the protocol, managed the literature analysis, and wrote the first draft of the manuscript. GK provided the search string and managed the literature search. NV, IP, AT and EV contributed to the study and supervised the work, from literature analysis to review of the final draft.

Conflict of interests

GM received travel grants from Janssen (unrelated to the present work). NV has received financial support for CME activities and travel funds from the following entities (unrelated to the present work): Angelini, Janssen-Cilag, Lundbeck, Otsuka. IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck (unrelated to the present work). AT received research support from Lundbeck and served as speaker for Angelini and Lundbeck (unrelated to the present work). EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Generalitat de Catalunya (PERIS), the Spanish Ministry of Science and Innovation (CIBERSAM), EU Horizon 2020, and the Stanley Medical Research Institute. GP acted as consultant to Lundbeck, Angelini, FB-Health; he received a scholarship / research support from Lundbeck and Angelini and he is a member of the speaker / advisory board of Sanofi-Aventis, Lundbeck, FB-Health, Angelini (unrelated to the present work). Other authors have no affiliation or financial interest in any organization that may constitute a conflict of interest.

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