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REVIEW

Treatment Implications of Predominant Polarity and the Polarity Index: A Comprehensive Review

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Abstract

Background: Bipolar disorder (BD) is a serious and recurring condition that affects approximately 2.4% of the global population. About half of BD sufferers have an illness course characterized by either a manic or a depressive predominance. This predominant polarity in BD may be differentially associated with several clinical correlates. The concept of a polarity index (PI) has been recently proposed as an index of the antimanic versus antidepressive efficacy of various maintenance treatments for BD. Notwithstanding its potential clinical utility, predominant polarity was not included in the DSM-5 as a BD course specifier.
Methods: Here we searched computerized databases for original clinical studies on the role of predominant polarity for selection of and response to pharmacological treatments for BD. Furthermore, we systematically searched the Pubmed database for maintenance randomized controlled trials (RCTs) for BD to determine the PI of the various pharmacological agents for BD.
Results: We found support from naturalistic studies that bipolar patients with a predominantly depressive polarity are more likely to be treated with an antidepressive stabilization package, while BD patients with a manic-predominant polarity are more frequently treated with an antimanic stabilization package. Furthermore, predominantly manic BD patients received therapeutic regimens with a higher mean PI. The calculated PI varied from 0.4 (for lamotrigine) to 12.1 (for aripiprazole).

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Conclusions: This review supports the clinical relevance of predominant polarity as a course specifier for BD. Future studies should investigate the role of baseline, predominant polarity as an outcome predictor of BD maintenance RCTs.

Keywords: bipolar disorder, maintenance, polarity index, predominant polarity, treatment

Introduction

Bipolar disorder (BD) is a chronic and debilitating mental disorder that affects approximately 2.4% of the general population (Belmaker, 2004; Merikangas et al., 2011). Bipolar disorder is associated with an increased risk of mortality due to suicide (Gonda et al., 2012) and co-morbid general medical conditions, mainly cardio-metabolic diseases (Fagiolini et al., 2008; Weiner et al., 2011). Bipolar disorder is characterized by recurring major depressive, manic (or hypomanic), and mixed episodes (Phillips and Kupfer, 2013). Lewis Judd and coworkers (2002, 2003) at the National Institute of Mental Health rated the affective symptoms of BD type I and II patients on a weekly basis. These authors demonstrated that BD patients spend approximately half of their lifetime symptomatic, mostly with depressive episodes/symptoms. However, germane to this thesis, the course of "manic depressive insanity" has been noted to be characterized by significant inter-individual variation (Kraepelin, 1921).

In the early 1960s, Leonhard collected data from 117 manic-depressive patients. Predominantly manic symptoms occurred in 17.9% of patients, while 25.6% presented with a predominantly depressive clinical course, and 56.4% had equally pronounced mania and depression (Leonhard, 1963). Angst (1978) collected data from a sample of 95 manic-depressive inpatients from 1959 to 1975. Based on this survey, Angst initially proposed the concept of predominant polarity. He observed that some patients have a nuclear type of illness (i.e. patients who show both mania and depression requiring hospital admission), while some patients have predominantly depressive (i.e. the patient required hospitalization for depression but had only hypomania) or manic (the patient required hospitalizations for mania, but had no or minor depression; Angst, 1978).

Recently, a renewed interest in the topic of predominant polarity as a course specifier for BD emerged in the literature, driven at least in part by a corresponding observation of the differential effects of newly-discovered bipolar agents on manic and depressive features (Osher et al., 2000; Colom et al., 2006; Rosa et al., 2008; Colom and Vieta, 2009; Baldessarini et al., 2012). Colom and colleagues (2006) proposed a threshold of at least two-thirds of lifetime depressive episodes for the definition of a depressive-predominant polarity, while at least two-thirds of past episodes would fulfill the criteria for mania/hypomania and define a manic-predominant polarity. However, the working definitions for predominant polarity have varied across studies (Osher et al., 2000; Daban et al., 2006; Baldessarini et al., 2012). Slightly more than half of BD patients exhibit a specific predominant polarity, while a significant proportion of BD patients have an undetermined predominant polarity.

A previous review suggested that the depressive-predominant polarity is more common than the manic-predominant polarity (Colom and Vieta, 2009). However, studies which incorporated exclusively type I BD patients found the opposite pattern (i.e. a higher prevalence of the manic-predominant polarity; Osher et al., 2000; Mazzarini et al., 2009; Pacchiarotti et al., 2011; Baldessarini et al., 2012). A confounder is that patterns of referral to tertiary centers where such studies are done reflect clinical acuity rather than community prevalence, providing a source of bias in such analyses.

Clinically-relevant correlates and outcomes for BD may be predicted by specific predominant polarity (i.e. depressive vs. manic). Depressive-predominant polarity has been associated with a depressive onset of illness (Rosa et al., 2008; Forty et al., 2009; Baldessarini et al., 2012), a delayed diagnosis of BD (Rosa et al., 2008; Baldessarini et al., 2012), type II BD, and an increased risk for suicidal acts (Colom et al., 2006; Gonzalez-Pinto et al., 2010; Baldessarini et al., 2012). Conversely, manic-predominant polarity is associated with a younger onset of illness (Gonzalez-Pinto et al., 2010; Baldessarini et al., 2012), a manic/psychotic first episode (Forty et al., 2009; Baldessarini et al., 2012), and a higher rate of substance abuse prior to the first episode (Colom et al., 2006; Popovic et al., 2014). Furthermore, a recent systematic review identified that a depressive-predominant polarity may be associated with a higher number of mixed episodes and with the presence of melancholic features (Carvalho et al., 2014).

Although a previous International Society of Bipolar Disorders (ISBD) taskforce on the nomenclature and course of bipolar disorder had concluded that the clinically-derived predominant polarity construct developed by Angst (1978) and operationalized by Colom et al. (2006) is a valid course specifier for BD, the recently-released DSM-5 did not include this concept in the criteria for bipolar disorders (APA, 2013). Current views on psychiatric nosology assert that clinical utility should guide validity (McGorry, 2013). Emerging evidence indicates that the concept of predominant polarity may influence the selection of maintenance pharmacological (Popovic et al., 2012, 2013; Nivoli et al., 2013) and psychological treatments (Popovic et al., 2013) for BD. Furthermore, the polarity index metric has been recently proposed to rank maintenance treatments for BD based on the relative antidepressive versus antimanic efficacies of interventions (Popovic et al., 2012).

In keeping with this view, the overarching aim of this article was to review the extant evidence on the possible clinical utility of the concept of predominant polarity for treatment selection in BD. Furthermore, we present clinical perspectives to highlight practical implications of predominant polarity. Limitations of the available evidence are also discussed. Finally, a research agenda is proposed.

Methods

A search was conducted using Pubmed/MEDLINE, EMBASE, and Web of Science computerized databases from inception of the project to December 8th, 2013. Search terms included polarity index, polarity, treatment, maintenance, predominant polarity, and bipolar disorder. Original studies on the treatment implications of predominant polarity (or the polarity index) were included in this comprehensive review.

Popovic and coworkers (2012) previously calculated the polarity index of maintenance pharmacological treatments of bipolar disorder based on a comprehensive search of data derived from randomized controlled trials (RCTs). In this report, we comprehensively searched the Pubmed/MEDLINE database for new maintenance RCTs of pharmacological treatments for BD from inception up to January 10th, 2014. The recalculated

polarity indexes of each drug (whether approved or not by regulatory agencies) are presented. The search terms bipolar disorder, mixed, mania, and bipolar depression were co-referenced with the term maintenance and the generic names of substances. Eligible studies were randomized, double-blind studies which compared mood stabilizers or antipsychotic drugs, alone or in combination with standard mood-stabilizing medications (e.g. lithium and valproate), with a placebo comparator. Included studies had a minimal duration of 24 weeks, in patients aged ≥18 years old. Exclusion criteria included small sample size (i.e. a median sample size <16.5 participants in each group; Popovic et al., 2012), a sample not exclusively composed of BD participants, and the lack of a placebo control. A manual search of reference lists of included studies augmented the search protocol. The citation tracking of included RCTs was searched in Google Scholar. No language restrictions were applied in this review.

The Concept of Polarity Index

Number needed to treat (NNT) is an effect size measure that is a recommended tool to summarize the results of BD trials (Martinez-Aran et al., 2008; Ketter et al., 2011). NNT can quantify the clinical relevance of a statistically significant trial outcome (Citrome, 2008). According to the most recent version of the CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines for the management of BD (Yatham et al., 2013), current first-line drug treatments for BD are: lithium, lamotrigine, divalproex, olanzapine, quetiapine, risperidone long-acting injection (LAI), aripiprazole, and the adjunctive use (with lithium or divalproex) of quetiapine, risperidone LAI, aripiprazole, or risperidone. It is noteworthy that some of these drugs are efficacious in preventing depressive episodes, but have limited efficacy for the prevention of manic episodes (for example, lamotrigine), while other drugs have a greater efficacy for the prevention of manic recurrences/relapses and a limited efficacy for the prophylaxis of major depressive episodes (for example, aripiprazole). Based on this fact, the concept of a polarity index (PI) was recently proposed (Popovic et al., 2012) as an attempt to rank the relative antimanic versus antidepressive prophylactic efficacy of distinct maintenance treatments for BD.

The PI is calculated by dividing the NNT for the prevention of depressive episodes by the NNT for the prevention of manic episodes (Popovic et al., 2012). Accordingly, an agent with a PI equal to 1 would have a balanced efficacy in the prophylaxis of both depressive and manic episodes. A drug with a PI > 1 would have stronger antimanic versus antidepressive prophylactic properties, while those with a PI < 1 are more effective in preventing depressive episodes than manic relapses/recurrences.

Polarity Index of Maintenance Pharmacological Treatments for BD

Our systematic search identified 19 potentially-eligible maintenance trials for BD. A clinical trial compared the efficacy of lamotrigine + placebo versus lamotrigine + divalproex for the prevention of depressive recurrences in 86 types I and II BD participants (Bowden et al., 2012). However, this study did not provide data on the prevention of (hypo) manic relapses. Thus, the polarity index could not be calculated. A recent RCT studied the effects of adjunctive N-acetlycysteine (NAC; 2 g/day) as maintenance treatment for BD (Berk et al., 2012). Participants were initially screened for bipolar depression and had received adjunctive NAC for 8 weeks (open-label phase); by the end of the acute phase all participants could be randomized to either

NAC or placebo for 24 weeks. These participants had low baseline symptoms, and the relatively low rates of recurrences possibly prevented the detection of drug differences. The authors concluded that the trial was a failed study instead of a negative one (Berk et al., 2012). Therefore, due to these limitations, this work was not included in this review. Two additional RCTs were identified in this updated systematic review and met inclusion criteria (Woo et al., 2011; Berwaerts et al., 2012). Thus, 18 studies satisfied inclusion criteria.

All investigations had an acute treatment phase, followed by a double-blind, controlled, maintenance phase. Some RCTs used a three-arm design: therefore, two comparisons were possible in these circumstances. Characteristics of included studies are summarized in Table 1.

The NNTs for the prevention of manic and depressives episodes for each agent, as well as the polarity index of each agent, are depicted in Table 2.

A predominantly antimanic polarity index was observed for aripiprazole monotherapy (PI = 12.1; Keck et al., 2007), followed by risperidone LAI (Quiroz et al., 2010; Vieta et al., 2012), aripiprazole adjunctive to lithium or divalproex (Marcus et al., 2011; Woo et al., 2011), olanzapine monotherapy (Tohen et al., 2006; Vieta et al., 2012), ziprasidone adjunctive to lithium or divalproex (Bowden et al., 2010), adjunctive risperidone LAI (Macfadden et al., 2009), and lithium (Prien et al., 1973; Bowden et al., 2000, 2003; Calabrese et al., 2003; Weisler et al., 2011). A polarity index favoring efficacy for the prevention of depressive episodes was observed for lamotrigine (pooled PI = 0.4; Bowden et al., 2003; Calabrese et al., 2003), followed by olanzapine combined with lithium or divalproex (Tohen et al., 2004), divalproex (Bowden et al., 2000), and oxcarbazepine combined with lithium (Vieta, Cruz, et al., 2008). Adjunctive quetiapine (Vieta, Suppes, et al., 2008; Suppes et al., 2009) and quetiapine monotherapy (Weisler et al., 2011) had polarity indexes closest to unit, suggesting a more balanced efficacy for the prevention of both manic and depressive recurrences.

Although the primary focus of this review is on the relationships of predominant polarity (and polarity index) for the selection of maintenance drug treatments for BD, it is noteworthy that a recent systematic review also determined the polarity index for evidence-based maintenance psychological interventions for BD (Popovic et al., 2013). In brief, most psychosocial interventions had a polarity index <1, indicating better efficacy for the prevention of depressive episodes, including cognitive behavioral therapy (PI ranging from 0.33 to 0.89), family-focused therapy (PI = 0.42), and psychoeducation (PI ranging from 0.73 to 0.78). Enhanced relapse prevention was equally effective for the prevention of depressive and manic episodes (PI = 1.0), whereas brief-technique driven interventions (PI = 3.36) and caregiver group psychoeducation (PI = 1.78) were more efficacious for the prevention of manic episodes (Popovic et al., 2013).

Clinical Studies on Predominant Polarity

This review had identified three original clinical studies in which the concept of predominant polarity was investigated either as a post hoc predictor of clinical response (Vieta et al., 2009) or as specifier associated with the selection of specific somatic treatments for BD (Nivoli et al., 2013; Popovic et al., 2014). These studies are summarized in Table 3.

A post hoc analysis of a previously published 8-week multi-center RCT which compared the olanzapine-fluoxetine combination with either olanzapine alone or placebo for the treatment of bipolar I depression (Tohen et al., 2003) investigated the

Table 1. Characteristics and Reported Outcomes of Maintenance RCTs Included in the Review.

Study characteristics				Trial Results			
				Manic Relapse		Depressive relapse	
Drug	Reference	Inclusion criteria (maintenance phase)	Duration (weeks)	Drug	Placebo	Drug	Placebo
Aripiprazole	Keck et al., 2007	Type I BD; YMRS ≤ 10; MADRS ≤ 13 No hospitalizations in previous 3 months	100	9/77 11.7%	23/83 27.7%	11/77 14.3%	13/83 15.7%
Aripiprazole adjunctive to lithium/divalproex	Marcus et al., 2011	Type I BD; YMRS ≥ 16 Current or recent manic/mixed episodeInadequate response to Li or divalproex YMRS ≥ 16 and ≤35% decrease in from baseline at 2 weeks	52	8/168 4.8%	25/169 14.8%	17/168 10.1%	22/169 13.0%
Aripiprazole adjunctive to divalproex	Woo et al., 2011	Type I BD current mixed or manic episode; YMRS ≤ 12 and MADRS ≤ 13 after a 6-wk open-label stabilization phase	24	3/40 7.5%	10/43 23.3%	3/40 7.5%	4/43 9.3%
Lamotrigine	Bowden et al., 2003	Type I BD; Current or recent (hypo) mania ≥ 1 additional (hypo) manic and 1 depressive episode in the past 3 years	76	16/59 27.1%	22/70 31.4%	8/59 13.6%	21/70 30.0%
Lamotrigine	Calabrese et al., 2003	Type I BD; Current or recent MDE and ≥1 additional (hypo) manic and 1 depressive episode in the past 3 years	72	38/215 17.7%	19/119 16.0%	77/215 35.8%	47/119 39.5%
Lithium	Bowden et al., 2003	Type I BD; Current or recent (hypo) mania ≥1 additional (hypo) manic and 1 depressive episode in the past 3 years	76	6/46 13.0%	22/70 31.4%	10/46 21.7%	21/70 30.0%
Lithium	Calabrese et al., 2003	Type I BD; Current or recent MDE ≥ 1 additional (hypo) manic and 1 depressive episode in the past 3 years	52	10/120 8.30%	19/119 16.0%	46/120 38.3%	47/119 39.5%
Lithium	Weisler et al., 2011	Type I BD; YMRS ≤ 12; MADRS ≤ 12; Acute current or recent manic, depressive, or mixed episodes treated with quetiapine	104	102/364 28.0%	291/404 72.0%	66/364 18.1%	186/404 46.0%
Lithium	Bowden et al., 2000	Type I BD; manic episode ≤ 3 months before randomization; MRS ≤ 11; DSS ≤ 13; GAS > 60, no serious suicidal risk	52	19/91 20.9%	21/94 22.3%	9/91 9.9%	15/94 16.0%
Lithium	Prien et al., 1973	Manic-depressive, manic type	24	23/101 22.8%	53/104 51.0%	9/101 8.9%	14/104 13.5%
Olanzapine	Tohen et al., 2006	Type I BD; YMRS ≤ 12; HDRS ≤ 8; 2 prior mixed or manic episodes in past 6 years	48	27/225 12.0%	44/136 32.3%	68/225 30.2%	53/136 39.0%
Olanzapine	Vieta et al., 2012	Type I BD; ≥2 mood episodes in the previous year	72	19/130 14.6%	52/132 39.4%	12/130 9.2%	23/132 17.4%
Olanzapine combined with lithium/divalproex	Tohen et al., 2004	Type I BD; YMRS ≤ 12; HDRS-21 ≤ 8	72	6/30 20.0%	11/38 28.95%	7/30 23.3%	15/38 39.5%
Oxcarbazepine combined with lithium	Vieta et al., 2008	Type I or II BD; YMRS ≤ 12; MADRS ≤ 20	52	4/26 15.4%	8/29 27.6%	3/26 11.5%	9/29 31.0%

(continued)

Table 1. Continued

Study characteristics				Trial Results			
				Manic Relapse		Depressive relapse	
Drug	Reference	Inclusion criteria (maintenance phase)	Duration (weeks)	Drug	Placebo	Drug	Placebo
Quetiapine	Weisler et al., 2011	Type I BD; YMRS ≤ 12; MADRS ≤ 12	104	121/404 30.0%	291/404 72.03%	65/404 16.1%	186/404 46.0%
Quetiapine combined with lithium/divalproex	Suppes et al., 2009	Type I BD; YMRS ≤ 10; MADRS ≤ 13	104	22/310 7.09%	61/313 19.5%	41/310 13.2%	102/313 32.6%
Quetiapine combined with lithium/divalproex	Vieta et al., 2008	Type I BD; YMRS ≤ 12; HDRS ≤ 12	104	36/336 10.7%	96/367 26.2%	26/336 7.7%	84/367 22.9%
Risperidone LAI	Quiroz et al., 2010	Type I BD; Recent manic/mixed episode or stable patients with ≥ 1 mood episode in past 4 months	96	22/140 5.7%	62/135 45.9%	20/140 14.3%	14/135 10.4%
Risperidone LAI	Vieta et al., 2012	Type I BD; ≥ 2 mood episodes in the previous year	~ 78	26/131 19.8%	52/132 39.4%	25/131 19.1%	23/132 17.4%
Risperidone LAI + treatment as usual	Macfadden et al., 2009	Type I BD ≥ 4 episodes in the past year	52	5/65 7.7%	12/59 20.3%	8/65 12.3%	11/59 18.6%
Valproate	Bowden et al., 2000	Type I BD; manic episode ≤ 3 months before randomization; MRS ≤ 11; DSS ≤ 13; GAS ≥ 60; no suicidal risk	52	33/187 17.6%	21/94 22.3%	12/187 12.3%	15/94 16.0%
Ziprasidone combined with Lithium/divalproex	Bowden et al., 2010	Type I BD; Current or recent manic/mixed episode; MRS ≥ 14	24	7/127 5.51%	14/111 12.6%	16/127 12.6%	16/111 14.4%
Paliperidone ER	Berwaerts et al., 2012	Type I BD; most recent episode manic or mixed; at least 2 previous mood episodes (one of which manic or mixed); participants who achieved remission on paliperidone in an acute/continuation phase were randomized to fixed-dose paliperidone ER or placebo	~ 171	31/146 21.0%	51/144 35.0%	35/146 24.0%	26/144 18.0%

BD, bipolar disorder; DSS, Depressive Syndrome Scale; GAS, Global Assessment Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, Major depressive episode; RCT, randomized controlled trial; YMRS, Young mania rating scale;

Table 2. Number Needed to Treat for the Prevention of Manic and Depressive Episodes and Polarity Index of Drugs Used for Maintenance treatment of Bipolar Disorder.

Treatment	NNT mania	NNT depression	Polarity Index
Aripiprazole monotherapy (Keck et al., 2007)	7.0	73.0	10.4
Aripiprazole adjunctive to lithium/divalproex-pooled (Marcus et al., 2011; Woo et al., 2011)	9.0	38.0	4.2
Lamotrigine-pooled (Bowden et al., 2003; Calabrese et al., 2003)	50.4	20.2	0.4
Lithium-pooled (Prien et al., 1973; Bowden et al., 2000, 2003; Calabrese et al., 2003; Weisler et al., 2011)	4.4	6.1	1.4
Olanzapine monotherapy-pooled (Tohen et al., 2006; Vieta et al., 2012)	4.4	17.5	4.0
Olanzapine combined with lithium/divalproex (Tohen et al., 2004)	11.2	6.2	0.5
Oxcarbazepine combined with lithium (Vieta et al., 2008)	8.2	5.1	0.6
Quetiapine monotherapy (Weisler et al., 2011)	2.4	3.3	1.4
Quetiapine combined with lithium/divalproex-pooled (Vieta et al., 2008; Suppes et al., 2009)	7.1	5.9	0.8
Risperidone LAI monotherapy-pooled (Quiroz et al., 2010; Vieta et al., 2012)	4.0	36.3	9.1
Adjunctive risperidone LAI (Macfadden et al., 2009)	7.9	15.8	2.0
Divalproex (Bowden et al., 2000)	21.3	10.5	0.5
Ziprasidone Adjunctive to lithium/divalproex (Bowden et al., 2010)	14.1	55.1	3.9
Paliperidone ER (Berwaerts et al., 2012)	8.0	17.0	N/A

NNT values in italic are negative, indicating that placebo was more effective than active treatment, although results of original trials did not reach statistical significance. When more than one RCT was available for a given treatment, calculations represent pooled results. LAI, long-acting injection; N/A, could not be calculated accurately as the NNT for the prevention of depression is negative; NNT, number needed to treat; RCT, randomized controlled trials.

relationship of predominant polarity as defined by a threshold of ≥2/3 of lifetime affective episodes of a given polarity (Colom et al., 2006) on treatment response (Vieta et al., 2009). Of the 833 participants initially enrolled in the trial, 788 subjects had both baseline and follow-up ratings so as to allow final outcome assessments; of these patients, 367/788 (46.6%) could be categorized as having had either a depressive-predominant polarity (269/788; 34.1%) or a manic-predominant polarity (98/788; 12.4%). The primary measure was a change in the Clinical Global Impression of severity of major depression (CGI-D; Spearing et al., 1997). The effect of predominant polarity as an outcome predictor was markedly dissimilar between men and women. In women there were no significant differences in CGI-D scores in accordance with predominant polarity (i.e. manic versus depressive), whereas in men the predominantly manic group has a significantly better outcome when compared to the predominantly depressive group. Furthermore, predominantly manic men had better outcomes compared to women with both predominant polarity types (Vieta et al., 2009).

The prescription patterns of a sample of 604 DSM-IV-TR BD patients attending the Bipolar Unit of Barcelona were investigated in a naturalistic study. A principal component analysis showed three factors: (i) an antimanic stabilization package, which was characterized by the use of classic thymoleptic medications (i.e. lithium, valproate, and carbamazepine), three atypical antipsychotics (clozapine, risperidone, and olanzapine), and electroconvulsive therapy; (ii) an antidepressive stabilization package, which included lamotrigine and other atypical antipsychotic agents (notably quetiapine); and (iii) an anti-bipolar II package, which included diverse antidepressants. Bipolar patients with a predominantly manic polarity were treated mainly with the antimanic stabilization package, whereas BD patients with a depressive-predominant polarity were more frequently treated with the antidepressive stabilization package (Nivoli et al., 2013). The anti-bipolar II package included mainly type II BD patients with a depressive-predominant polarity (Nivoli et al., 2013).

Popovic and colleagues (2014) studied a sample of 604 DSM-IV-TR BD patients, of which 257 presented a clear predominant polarity type (n = 143; 55.6% had a depressive-predominant polarity and n = 114; 44.4% had a manic-predominant polarity; Colom et al., 2006). The total polarity index (calculated as mean value of polarity index of all prescribed mood stabilizers and antipsychotics in each patient) were significantly higher in the predominantly manic group. Moreover, the polarity index of antipsychotics and mood stabilizers taken separately were also higher in the manic-predominant polarity group. The use of antidepressants, lamotrigine, and benzodiazepines was more prevalent in the depressive-predominant polarity group (Popovic et al., 2014).

D2 Receptor Binding Affinity and Polarity Index of Atypical Antipsychotics

Brugue and Vieta (2007) had previously hypothesized that a lower D2 receptor occupancy would be more more relevant than a greater 5-HT(2) receptor action to the efficacy of atypical antipsychotics for the acute treatment of bipolar depression Herein we examined the relationship of D2 receptor affinities (Richtand et al., 2007) and the polarity index of atypical antipsychotrics in monotherapy (Table 4). Overall, we found that the higher the D2 receptor binding affinity, the lower the PI of different atypical antipsychotics in monotherapy. Aripiprazole did not seem to follow the same pattern: in fact, the mechanism of action of aripiprazole is rather complex (Mailman and Murthy, 2010). Once thought to primarily act as a partial agonist at D2 receptors, new data support that aripiprazole may act either as an antagonist or as an agonist at distinct subpopulations of D2 receptors in a process referred to as functional selectivity (Mailman and Murthy, 2010). These unique mechanisms may explain the divergent findings related to D2 binding affinity and the PI of this compound.

Clinical Perspectives

In spite of the fact that the efficacy of antidepressant drugs for the acute and maintenance treatment of BD is one of the most long-standing controversial topics in the literature (Gitlin, 2012; Malhi,

Table 3. Characteristics and Main Finsdings of Clinical Studies on Predominant Polarity (PP).

Reference	Sample characteristics	Study Design	Definition of predominant polarity	Main Findings
Vieta et al., 2009	833 type I BD participants in a depressive episode; 788 had baseline and follow-up ratings; DSM-IV criteria	Multicenter RCT Olanzapine, OFC and placebo	≥2/3 of lifetime episodes of a given polarity	34.1% (n = 269) had a DPP and 12.4% (n = 98) had a MPP. Psychotic features were more common in the DPP. Rapid cycling was more common in the MPP (only in men). In men, a MPP was associated with a greater likelihood for acute treatment response.
Nivoli et al., 2013	604 BD participants (types I, II and NOS); DSM-IV; 332 (55%) were females; 407 (67.4%) had type I BD and 201 (32.6%) had type II or type NOS BD; 314 (52.0%) had experienced a psychotic mood episode and 117 (19.4%) had rapid cycling; Spain	Observational	≥2/3 of lifetime episodes of a given polarity	Principal component analysis revealed that 3 basic treatment packages: antimanic stabilization package, antidepressant stabilization package, and anti-bipolar II package. Antimanic stabilization package was associated with a MPP, while the antidepressant stabilization package was associated with the DPP.
Popovic et al., 2013	604 type I or II BD participants; included 257 participants with a PP; DSM-IV-TR; Spain	Observational	≥2/3 of lifetime episodes of a given polarity	44.4% (n = 114) had a MPP and 55.6% (n = 143) had a DPP. Polarity index of the therapeutic regimen was significantly higher for the MPP group. The MPP group had higher use of olanzapine, risperidone, and typical antipsychotics. The DPP group had higher use of lamotrigine, antidepressants TCAs, SSRIs, SNRIs, and benzodiazepines. The MPP group had significantly younger age of disease onset, younger age at first hospitalization, and higher hospitalization rate.

BD, bipolar disorder; DPP, depressive-predominant polarity; MPP, manic-predominant polarity; OFC, olanzapine-fluoxetine combination; RCT,; SSRIs, selective serotonina reuptake inhibitors; SNRIs, selective norepinephrine reuptake inhibitors; TCAs, trycyclic antidepressants.

Table 4. Polarity Index Based on Monotherapy of Atypical Antipsychotics and Dopamine D2 Receptors.

Drug	NNT Depression	NNT Mania	Polarity Index	K_i (nM)*
Aripiprazole[a]	73.0	7.0	10.4	0.95
Risperidone (LAI)[b]	36.3	4.0	9.1	4.9
Olanzapine[c]	17.5	4.4	4.0	72
Quetiapine[d]	2.4	3.3	1.4	567

*K_i values obtained from Richtand et al. (2007); [a]Data from Keck et al. (2007); [b]Data from Quiroz et al. (2010) and Vieta et al. (2012); [c]Data pooled from Tohen et al. (2006) and Vieta et al. (2012); [d]Data obtained from Vieta et al. (2012). K_i dissociation constant; LAI, long-acting injection; NNT, number needed to treat.

2012), in part due to an inconsistent evidence base (Vazquez et al., 2011), epidemiological surveys indicate that antidepressant drugs are widely employed in the management of BD, mainly for the management of acute bipolar depression episodes (Post et al., 2011; Grande et al., 2013; Llorca et al., 2013). This status quo resulted in a recent ISBD consensus panel on the use of antidepressant in BD (Pacchiarotti et al., 2013), based to a large degree on expert consensus through the Delphi method. However, the evidence reviewed thus far suggests that clinicians from tertiary mood disorder services consider the patient's predominant polarity while prescribing antidepressants.

Given the extant evidence base showing that maintenance agents differ in their efficacy across the two poles, the predominant polarity of a given patient is probably considered by clinicians more broadly when selecting both acute and long-term maintenance treatments. As stated before, there are concerns regarding the use of antidepressants for the long-term treatment of BD. Notwithstanding concerns about the so-called antidepressant-induced manic switch, this aspect remains controversial, as a clear causal relationship linking antidepressant exposure to the precipitation of mania is not firmly established (Licht et al., 2008).

Discussion

Predominant polarity predicts several clinical correlates in BD, as reviewed elsewhere (Colom and Vieta, 2009; Baldessarini et al., 2012). The present review strongly suggests that the concept of predominant polarity is useful for the selection of appropriate maintenance treatments for BD. In keeping with this view, it is important to consider that one should consider the clinical utility of a given specifier to endorse its inclusion in current psychiatric nosology (McGorry, 2013).

This review demonstrates that different maintenance drug treatments for BD may have differential efficacies for the prevention of manic versus depressive episodes. This systematic literature search updates a previous review (Popovic et al., 2012). We had identified two additional eligible RCTs (Woo et al., 2011; Berwaerts et al., 2012). Importantly, paliperidone's PI could not be calculated, as the NNT for the prevention of depressive episodes was negative. Hence, most atypical antipsychotics have a greater efficacy for the prevention of manic episodes, while quetiapine has a more balanced efficacy for the maintenance treatment of BD.

The published post hoc analysis of the 8-week RCT, which studied the olanzapine-fluoxetine combination versus both olanzapine alone and placebo in the acute treatment of bipolar depression (Vieta et al., 2009), found that a manic-predominant polarity predicted efficacy specifically for male participants. While these data suggest that predominant polarity may influence acute treatment responses in BD, the limitations of this study do not allow the establishment of firm directions. In fact, most patients in that trial had a 2.7-fold excess for the depressive-predominant polarity when compared to a manic-predominant polarity, as expected from a recruited sample for a bipolar depression trial. Furthermore, this post hoc analysis could not include all participants of the original trial (Tohen et al., 2003). Thus, one might argue that this analysis did not have adequate power to detect additional inferences, as acknowledged by the authors (Vieta et al., 2009). Consequently, the role of predominant polarity for the prediction of acute treatment responses in BD remains, to a large extent, an open question.

Two naturalistic clinical studies from the same research group (Nivoli et al., 2013; Popovic et al., 2014) suggest that the concept of predominant polarity may play a decisive role for the selection of maintenance pharmacological treatments for BD. The first report showed that patients with a predominantly manic polarity would be treated in the majority circumstances with an antimanic stabilization package, while patients with a depressive-predominant polarity would be mainly treated with an antidepressive stabilization package (Nivoli et al., 2013). The other study viewed the data from a different angle. Patients with a manic-predominant polarity were treated with a therapeutic regimen with a higher mean polarity index, while patients with a depressive-predominant polarity were treated with agents

with an overall lower PI (Popovic et al., 2014). Despite the fact that these data may provide some support for the wise everyday care of BD, it should be interpreted in light of several limitations. First, the data came from a single center (i.e. the Barcelona BD Center). Thus, these data may not reflect the practice at other centers or settings. Furthermore, part of the data was collected retrospectively. Therefore, it should be replicated in prospective multi-center studies to establish more conclusive evidences on the true role of predominant polarity (and the PI) for the selection of maintenance treatments for BD. Lastly, there is a degree of circularity in the argument: clinicians choose treatments they believe to be most useful for an individual's pattern of illness, and it is unsurprising that prescription patterns reflect this.

Although intuitive and easy-to-use, the PI has been criticized as imperfect by some investigators (Alphs et al., 2013). First, the PI does not offer a credible interval. Second, there are variations in clinical and socio-demographic characteristics of included participants across different trials (for example, age, sex, previous exposure to treatment, comorbidities, number of previous affective episodes, etc). Third, the calculation of the PI would be impossible when confidence intervals of NNTs for the prevention of either depressive or manic episodes includes zero. Lastly, it is relativistic, not absolute; an agent that has both potent antimanic and anti-depressive effects would have the same PI as an agent weak in both poles. We agree with the authors that no simple metric is sufficient for the complex evidence-based final choice of a given maintenance treatment for BD. For instance, consider that a drug with a NNT for prevention of mania of 4.0 and a NNT for the prevention of depression of 2.0 would have a PI = 2.0, whereas a drug with a NNT for the prevention of mania of 8.0 and a NNT for the prevention of depression of 2.5 would have the same PI = 3.2. This would induce the clinician to prescribe the latter drug for use in the maintenance treatment of a predominantly manic patient. Clearly, this choice based solely on the PI would be misleading. We argue here that the PI provides useful, albeit imperfect, information for the choice of a maintenance treatment of BD for a given patient. However, no metric should be used in isolation. For example, the PI should be used while considering the NNT and NNH (i.e. number needed to harm), and also taking into account the methodological quality (and risk of bias) of isolated RCTs that contributed to the PI, NNT, and NNH estimations. Furthermore, the calculated PI for divalproex and oxcarbazepine should be interpreted with extreme caution because pivotal trials did not evidence superiority over placebo (Bowden et al., 2000; Vieta, Cruz, et al., 2008).

An important limitation of the current concept of predominant polarity (and the polarity index) refers to the fact that mixed episodes are not contemplated. Mixed episodes have been increasingly emphasized in the current nosology of BD (Berk et al., 2006; APA, 2013; Castle, 2014). Therefore, future studies should investigate the possible existence of a predominantly mixed type of BD. This awaited evolution in the concept of predominant polarity may provide a substrate to add potentially valuable pieces of information to the selection of the limited alternatives available for the treatment of mixed affective episodes (Fountoulakis et al., 2012). A first approach to this concept has been conducted (Pacchiarotti et al., 2011).

Conclusions

The present review concludes that the concepts of predominant polarity and polarity indexes provide clinically useful information for the selection of maintenance treatments for BD. Furthermore, there are important unanswered questions

for further research and this opens an important debate for the incorporation of these constructs in current psychiatric nosology. If one considers clinical utility as a determinant for the construction of nosology, this work concludes that there probably is sufficient evidence for the incorporation of predominant polarity as a course specifier for BD. However, clinical trials (both acute and maintenance) may include the baseline determination of predominant polarity as a potential predictor of response. Pooled analyses would ultimately provide a stronger evidence base. However, there are no published studies that we are aware of investigating biological leads (e.g. genetic polymorphisms, neuropsychological tests, and neuroimaging correlates) related to predominant polarity. Considering emerging neuroscience-based models of psychiatric nosology (such as the National Institute of Mental Health Research Domain Criteria), further investigations are needed in this particular field (Insel et al., 2010; Cuthbert and Insel, 2013).

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