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Review Article

Predominant polarity as a course specifier for bipolar disorder: a systematic review

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ABSTRACT

Background: Predominant polarity (PP) is a proposed course specifier for bipolar disorder, which was not incorporated in the DSM-5 as a descriptor for the nosology of bipolar disorder (BD). Here we perform a systematic review of original studies about PP.

Methods: A computerized search of MEDLINE/Pubmed, EMBASE and Web of Science databases from inception to October 6th, 2013 was performed with keywords, including ‘bipolar disorder’, ‘polarity’ and ‘predominant polarity’.

Results: A total of nineteen studies met inclusion criteria. A unifying definition and conceptualization for PP is lacking. A PP is found in approximately half of BD patients. Most studies that included type I BD patients found the manic PP to be more prevalent, while studies that included type II BD participants found a higher prevalence of depressive PP. The depressive PP has been consistently associated with a depressive onset of illness, a delayed diagnosis of BD, type II BD and higher rates of suicidal acts. The manic PP is associated with a younger onset of illness, a first episode manic/psychotic and a higher rate of substance abuse. Evidence suggests that PP may influence responses to acute treatment for bipolar depression. Furthermore, evidences indicate that PP should be considered for the selection of maintenance treatments for BD.

Limitations: There are few prospective studies on PP. There were disparate definitions for PP across studies.

Conclusions: The concept of PP provides relevant information for clinicians. Future studies should investigate the genetic and biological underpinnings of PP.

Key Words: Bipolar disorder; predominant polarity; depression; mania; treatment; diagnosis

1. Introduction

Bipolar disorder is a severe, chronic and disabling mental illness, which affects approximately 2.4% of the general population worldwide (Belmaker, 2004; Merikangas et al., 2011). The clinical course of BD is typified by recurring major depressive episodes as well as (hypo) manic and mixed episodes (Phillips and Kupfer, 2013). The seminal studies carried out by Lewis Judd and coworkers at the National Institute of Mental health (NIMH) demonstrate that BD patients spend slightly more than half their lifetime suffering from affective symptoms, mostly depressive episodes/symptoms (Judd et al., 2003b). However, since Kraepelin, BD has been regarded as an illness whose symptomatic expression and long-term clinical evolution is characterized by significant inter-individual variation (Kraepelin, 1921; Roy-Byrne et al., 1985).

In the early 1960s, Leonhard reported the course in 117 bipolar patients. Predominant manic colouring occurred in 17.9%, predominant depressive in 25.6% and equally pronounced manic and depressed in 56.4% (Leonhard, 1963). Angst followed-up (from 1959 to 1975) a representative sample of 95 bipolar ‘manic-depressive’ inpatients (Angst, 1978). Based on this study, Angst formulated the concept of predominant polarity (Angst, 1978). Accordingly, it was observed that some patients have a ‘nuclear’ type of the illness (i.e., patients who show both mania and depression requiring hospital admission; type MD), while some patients have predominantly depressive (i.e., the patient required hospitalization for depression but had only hypomania; type Dm) and manic (i.e., the patient required hospitalization for mania, but has no or minor depression; type Md) (Angst, 1978).

More recently, the literature had witnessed a renewed interest in this topic (Baldessarini et al., 2012b; Colom and Vieta, 2009; Osher et al., 2000). Colom and colleagues suggested a threshold as at least two-thirds of lifetime major depressive episodes for the definition of a

depressive predominant polarity, while at least two-thirds of past episodes fulfilling criteria for hypomania/mania defined a manic predominant polarity (Colom et al., 2006a). Notwithstanding attempts to operationalize the concept of predominant polarity (Pacchiarotti et al., 2013; Rosa et al., 2008; Vieta et al., 2009), the definition and criteria for predominant polarity have been mixed (Baldessarini et al., 2012b; Daban et al., 2006; Osher et al., 2000). Previous studies indicate that a predominant polarity can be identified in more than half of the patients (Baldessarini et al., 2012b; Rosa et al., 2008). The majority of investigations suggest that a depressive predominant polarity is the most frequent type (Gonzalez-Pinto et al., 2010; Nivoli et al., 2011b; Rosa et al., 2008). However, some studies, which incorporated samples of exclusively type I BD patients had found the opposite pattern (i.e., a higher prevalence of the manic predominant polarity) (Baldessarini et al., 2012b; Osher et al., 2000). Clinical correlates may vary as a function of the predominant polarity subtype (i.e., depressive versus manic). For example, the depressive predominant polarity has been associated with a depressive onset of BD (Colom et al., 2006b; Etain et al., 2012), higher number of suicidal attempts (Baldessarini et al., 2012b; Gonzalez-Pinto et al., 2010), and a greater interval from the commencement of affective symptoms to the proper diagnosis of BD (Baldessarini et al., 2012b; Rosa et al., 2008). The manic predominant polarity type has been associated with an earlier age of onset (Colom et al., 2006b; Gonzalez-Pinto et al., 2010), more psychotic symptoms (Popovic et al., 2013b) and a higher number of hospitalizations (Baldessarini et al., 2012b; Popovic et al., 2013b).

Accumulating evidence suggests that the concept of predominant polarity may have clinical relevance for the management of BD (Alessandra et al., 2013; Popovic et al., 2012; Popovic et al., 2013a; Vieta et al., 2009). For instance, Popovic and coworkers proposed a 'polarity index' to guide treatment choices for maintenance pharmacological and psychological treatments for BD (Popovic et al., 2012; Popovic et al., 2013a). The polarity index (PI)

represents the ratio of the number needed to treat (NNT) for the prevention of depression and the NNT for prevention of mania (Popovic et al., 2012). A naturalistic study indicated that the net polarity index of ongoing treatment for BD was consistent with the patient's predominant polarity (i.e., participants with a manic predominant polarity tended to have maintenance treatment with lower PI when compared with the ones with a depressive predominant polarity) (Popovic et al., 2013b).

A Taskforce on the nomenclature and course of BD sponsored by the International Society of Bipolar Disorders (ISBD) had concluded that the clinically derived predominant polarity construct developed by Angst and operationalized by Colom et al. (Colom et al., 2006b) is a valid course specifier for BD (Tohen et al., 2010). Nevertheless, the DSM-5 did not include 'predominant polarity' as course specifier for BD (Association, 2013). Therefore, the overarching aim of this systematic review is to examine original studies which incorporated the concept 'predominant polarity' using disparate criteria to provide an evidence-based assessment of the reliability of this putative BD course descriptor. Furthermore, strengths and limitations of the available data are discussed and future research directions are presented.

2. Method

Original reports investigating predominant polarity in BD samples were located through searches in Pubmed/MEDLINE, EMBASE and Web of Science from inception to October 6th, 2013. No language restrictions were applied. The Pubmed database was searched using the search terms ("bipolar disorder"[MeSH Terms] OR ("bipolar"[All Fields] AND "disorder"[All Fields]) OR "bipolar disorder"[All Fields] OR ("bipolar"[All Fields] AND "disorders"[All Fields]) OR "bipolar disorders"[All Fields]) AND "polarity"[All Fields] OR (predominant[All Fields] AND polarity[All Fields]). The EMBASE database was searched using the search terms

((bipolar AND disord* AND polarity) OR predominant) AND polarity (extensive search). The Web of Science database was searched using the search terms Bipolar disorders AND polarity OR predominant polarity. This systematic review included retrospective, cross-sectional, naturalistic and prospective studies involving patients with bipolar disorder diagnosed in accordance to the 10th edition of the International Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (from DSM-III-R to DSM-5) (Association, 2013). Included studies had to provide data where the predominant polarity of included participants could be extracted or inferred as a fraction of episodes of a given polarity ((hypo) manic or depressive) per years at risk. Furthermore, to be eligible for inclusion the study should have an appropriate sample size (i.e., ≥ 70 BD participants). This review followed the recommendations of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2010). Two investigators (AFC and KNF) screened the titles/abstracts for eligibility. Disagreement was resolved through consensus. Selected articles were assessed for eligibility after full-text review by the same authors (AFC and KNF). Again, disagreement was resolved through consensus.

3. Results

Of 1808 titles/abstracts identified, 1764 were excluded after title/abstract review. Ten additional studies were obtained from other sources (i.e., manual searches of reference lists of included articles), leaving 54 studies selected for full-text review. Following consensus, 19 unique studies were found eligible for this systematic review (Table 1 and Figure 1). The data provided by the included reports are organized in domains: a) Conceptualization of predominant polarity; b) Prevalence rate; c) Socio-demographic correlates; d) Clinical correlates; e) Relationship with long-term course and outcome and f) Implications for the management of bipolar disorder. Subdomains were also utilized to further organize the data (Table 2).

a) Conceptualization and definition of predominant polarity

There were different definitions for predominant polarity across studies. Several studies considered the simple definition of having more lifetime episodes of a given polarity to determine the predominant polarity (i.e., depressive vs. manic) (Colom et al., 2006a; Forty et al., 2009; Gonzalez-Pinto et al., 2010; Henry et al., 1999; Osher et al., 2000). Colom and coworkers had arbitrarily conceptualized predominant polarity as having at least two-thirds of lifetime episodes in a given polarity (Colom et al., 2006a). Since then, several investigations had followed this definition (Garcia-Lopez et al., 2009; Mazzarini et al., 2009; Nivoli et al., 2011b; Pacchiarotti et al., 2013; Rosa et al., 2008; Vieta et al., 2009). Importantly, Baldessarini and colleagues compared the two aforementioned criteria for predominant polarity in their multicenter investigation of type I BD patients (N=928) (Baldessarini et al., 2012b). These investigators had found that expanding the Colom et al. criteria (Colom et al., 2006a) to the broader definition (i.e., > 50.0% of episodes of a given polarity) added increased the proportion of categorizable patients as expected, but did not considerably add in detecting differences in clinical correlates between predominant-polarity subgroups (Baldessarini et al., 2012b).

b) Prevalence

Across included studies, the prevalence of a predominant polarity in samples of BD patients varied between 42.4-71.8% (median value: 52.7%). A depressive predominant polarity was found in 17.0-34.1% (median value: 21.4%) of the BD samples, a manic preponderance was observed in 12.4-55.0% of participants (median value: 26.0%) (Table 2). It is noteworthy that across studies that include type II BD, a preponderance of the depressive predominant polarity is a replicated observation (Colom et al., 2006a; Goikolea et al., 2007; Popovic and Vieta, 2013; Rosa et al., 2008). Conversely, studies that included only type I BD participants report higher prevalence of the manic predominant polarity (Baldessarini et al., 2012a; Mazzarini et al., 2009;

Osher et al., 2000; Pacchiarotti et al., 2013), whereas studies that included a broader spectrum of bipolar patients tended to report a higher prevalence of the depressive predominant polarity (Alessandra et al., 2013; Garcia-Lopez et al., 2009; Popovic and Vieta, 2013).

c) Socio-demographic correlates

The depressive predominant polarity is associated with the female gender in some (Baldessarini et al., 2012b; Nivoli et al., 2011a) , but not all studies (Colom et al., 2006a; Gonzalez-Pinto et al., 2010; Mazzarini et al., 2009; Osher et al., 2000; Rosa et al., 2008). The depressive predominant polarity group has been associated with a greater likelihood of having been married (Baldessarini et al., 2012b; Gonzalez-Pinto et al., 2010). Notwithstanding a recent study suggested that the male sex is associated with the manic predominant polarity (Popovic et al., 2013b); however, most studies have not replicate this finding (Baldessarini et al., 2012b; Colom et al., 2006a; Osher et al., 2000; Vieta et al., 2009).

d) Clinical correlates

d.1) Age of onset and first episode polarity

A manic predominant polarity was associated with a younger age of illness onset in at least three studies (Baldessarini et al., 2012b; Gonzalez-Pinto et al., 2010; Popovic et al., 2013b). A first episode of depressive polarity was associated with a depressive predominant polarity across several studies (Baldessarini et al., 2012b; Forty et al., 2009; Popovic et al., 2013b; Rosa et al., 2008). The largest study to date had suggested that a mixed onset of illness is also associated with a depressive predominant polarity (Baldessarini et al., 2012b). However, this possible association was not investigated in the majority of included studies. A manic onset of illness was associated with a manic predominant polarity in three studies (Baldessarini et al., 2012b; Forty et al., 2009; Popovic et al., 2013b).

d.2) Relationship with suicidality and substance use disorders

A depressive predominant polarity is consistently associated with a higher number of suicide attempts across investigations (Baldessarini et al., 2012b; Colom et al., 2006b; Gonzalez-Pinto et al., 2010; Popovic et al., 2013b). For example, a study involving 124 type I BD participants demonstrated an association between suicidal ideation and the depressive predominant polarity (Mazzarini et al., 2009). However, this finding has not been replicated. Baldessarini et al. (Baldessarini et al., 2012b) reported in a pooled analysis that when mixed-states were added to a broader category of ‘depression-plus-mixed’ predominant polarity the association with suicidal acts nearly doubled, from relative risk of 2.48 (95% CI: 0.41-14.8, $z=0.99$, $P=0.32$) to 4.62 (95% CI: 2.16-9.89, $z=3.95$, $P < .0001$).

A history of substance abuse preceding first episode has been reported to correlate with a manic predominant polarity (Colom et al., 2006b; Popovic et al., 2013b). The prospective study by González-Pinto et al. (Gonzalez-Pinto et al., 2010) followed 120 type I BD patients for up to ten years and a significant decrease in alcohol/other drug abuse in the manic predominant polarity group was observed (Gonzalez-Pinto et al., 2010).

d.3) Association with co-occurring mental disorders

Colom et al. observed no differences between the manic- versus depressive predominant groups regarding differences in co-occurring DSM-IV axis I and II mental disorders (Colom et al., 2006b). Subsequent studies replicated these findings (Baldessarini et al., 2012b; Mazzarini et al., 2009; Nivoli et al., 2013; Popovic et al., 2013b). Another study did not find differences in co-occurring personality disorders as a function of the type of predominant polarity (Murru et al., 2011). Koyuncu et al. specifically studied the prevalence and clinical correlates of co-occurring DSM-IV obsessive compulsive disorder (OCD) in a sample of 216 BD participants; these

authors did not identify differences regarding manic- versus depressive predominant polarity groups (Koyuncu et al., 2010).

d.4) Other clinical correlates

The depressive predominant polarity has been positively linked to the number of years from the commencement of affective symptomatology to a proper diagnosis of BD (Baldessarini et al., 2012b; Rosa et al., 2008). The depressive predominant polarity also is associated with a type II BD diagnosis (Colom and Vieta, 2009; Colom et al., 2006b; Goikolea et al., 2007; Popovic et al., 2013b; Rosa et al., 2008). The presence of melancholic features is also associated with the depressive predominant polarity (Colom et al., 2006b; Popovic et al., 2013b).

A manic predominant polarity is associated with a higher number of hospitalizations in most (Colom and Vieta, 2009; Gonzalez-Pinto et al., 2010; Popovic et al., 2013b), but not all studies (Mazzarini et al., 2009). A manic predominant polarity has been associated with a first illness episode with psychotic features across studies (Baldessarini et al., 2012b; Popovic et al., 2013b).

The prevalence of an ever occurring rapid cycling pattern (defined as the occurrence of at least four yearly affective episodes during the course of the illness) according to predominant polarity groups was investigated across several studies (Baldessarini et al., 2012b; Nivoli et al., 2013; Popovic et al., 2013b; Rosa et al., 2008; Vieta et al., 2009). In general studies did not verify differences in the occurrence of rapid cycling as a function of predominant polarity. Vieta et al. found that a rapid cycling was associated with the manic predominant polarity, specifically in men (Vieta et al., 2009).

A DSM-IV seasonal pattern of illness has been linked to the depressive predominant polarity (Colom et al., 2006b; Goikolea et al., 2007). However, this finding was no longer

significant following multivariable adjustment (Goikolea et al., 2007). Furthermore, another study did not replicate this finding (Popovic et al., 2013b).

The manic predominant polarity has been negatively associated with a depressive affective temperament (as operationalized by Akiskal & Mallya) (Akiskal and Mallya, 1987; Henry et al., 1999). However, another study did not find evidence for differences in predominant affective temperaments as a function of the type of predominant polarity (Mazzarini et al., 2009).

A depressive predominant polarity is associated with a higher number of mixed episodes (Baldessarini et al., 2012b; Colom et al., 2006b). A sample of 134 type I BD patients were studied and categorized in accordance to their pattern of excited ‘mixed-like’ episodes in three groups: lifetime history of pure manic episodes without mixed features; lifetime history of both manic and mixed episodes and lifetime history of exclusively mixed, but not manic episodes. Following multivariable adjustment for potential confounders, a history of pure mixed episodes was associated with higher proportions of depressive predominant polarity (Pacchiarotti et al., 2011). A principal component analysis of the 24-item brief psychiatric rating scale (BPRS) (Ventura et al., 2000) in a consecutive sample of 187 type I BD inpatients (Pacchiarotti et al., 2013) was performed. Five factors explained 71.9% of the variance. A ‘mixture’ factor included anxiety, tension, suicidality, motor hyperactivity and excitement (Pacchiarotti et al., 2013). This ‘mixture’ factor of the BPRS was independently associated with the depressive predominant polarity.

e) Treatment implications

Vieta et al. performed a *post hoc* analysis of the role of predominant polarity as an outcome predictor in a 8-week, multicenter, randomized controlled trial (RCT) of olanzapine, the olanzapine-fluoxetine combination (OFC) or placebo in sample of 788 depressed participants

with baseline and follow-up assessments (Vieta et al., 2009). A manic predominant polarity was associated with a greater likelihood for response by the end of the trial (Vieta et al., 2009).

A sample of 604 DSM-IV-TR BD participants was studied in a naturalistic study. A principal component analysis of management approaches revealed three main factors: (i) an ‘antimanic stabilization package’, which was characterized by the use of classic mood stabilizers (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 antipsychotics (e.g., quetiapine) and (iii) a ‘anti-bipolar II package’, which included antidepressants of various classes (Nivoli et al., 2013). A manic predominant polarity was associated with treatment with the ‘antimanic stabilization package’, whereas the depressive predominant polarity was associated with treatment 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).

4. Discussion

The present systematic review confirms that a specific predominant polarity can be defined in approximately half of BD patients. Importantly, previous narrative reviews suggested that the depressive predominant polarity is the most common subtype (Colom and Vieta, 2009). However, our systematic review demonstrates that the manic predominant polarity is more common than the depressive predominant polarity in studies that included type I BD participants, including the largest study performed on the subject, which included 928 international type I BD participants (Baldessarini et al., 2012b), while the opposite pattern (i.e., a higher percentage of the depressive predominant polarity) emerged in samples enriched with type II BD participants. These results are in contrast to prospective studies, which rated affective symptoms weekly, which had found that depression dominates the clinical course of both type I and type II BD

(Judd et al., 2003a; Judd et al., 2002; Roy-Byrne et al., 1985). This may reflect biases in the studies included in this systematic review. Most studies herein were carried out in specialized centers, which capture highly selected populations, and center differences, such as inpatient versus outpatient or primary care settings are a powerful determinant of casemix.

There is a long delay between the first appearance of affective symptoms and the ultimate diagnosis of BD (Drancourt et al., 2013). Thus, possibly the determination of the lifetime affective predominance was subjected to intrinsic recall bias across studies. For example the proper determination of the number of hypomanic episodes may prove to be difficult to ascertain. Furthermore, the recruitment process of included participants was not mentioned in several studies, indicating that a sample selection bias may partly explain discrepancies. However, the seminal prospective studies (Judd et al., 2003a; Judd et al., 2002) considered sub-syndromal depressive symptoms, which are not incorporated in the concept of predominant polarity (Colom et al., 2006b), which may also play a role in the discrepant findings. Inter-episodic sub-syndromal morbidity, specially dysthymia and dysphoria, are relevant in the course of BD (Baldessarini et al., 2010) and are not taken into account in the determination of the predominant polarity type, reflecting a possible limitation of this putative BD course specifier.

The concept of predominant polarity predicted several meaningful correlates in BD. This systematic review did not reveal clear associations between socio-demographic variables as a function of predominant polarity across investigations. Conversely, important clinical patterns emerged according to predominant polarity subtypes. The depressive predominant polarity is associated with type II BD, a depressive onset of illness, a higher rate of suicidal acts, a delayed diagnosis of BD, a higher number of mixed episodes and melancholia. The manic predominant polarity has been consistently associated with a manic/psychotic illness onset, a younger age of onset and a higher rate of alcohol/other drug abuse. It is noteworthy that included studies did not

specify which psychoactive substances would be specifically associated with a particular polarity predominance. These replicated findings should be interpreted with caution as some, but not all studies performed multivariable adjustment for confounders. Despite these limitations, these findings suggest that efforts should be directed towards the recognition of patients with depressive predominant polarity as a delayed diagnosis may result in worse prognosis and treatment resistance as a result of neuroprogressive processes (Berk et al., 2011). Furthermore, a depressive predominant polarity, especially when associated with mixed episodes should prompt a closer monitoring of suicidal risk across treatment (Gonda et al., 2012). The manic predominant polarity should prompt a closer investigation of co-morbid substance use disorders with important prognostic implications for BD (Post and Kalivas, 2013). Importantly, Angst and colleagues recently reported mortality causes for 403 mood disorders patients followed up since their first hospital admission (Angst et al., 2013). Mortality due to suicide was associated with the depressive component of mood disorders (i.e., patients with major depression, type II BD and the nuclear/MD type BD I had significantly higher suicide rates than Md type I BD participants), while patients with mania (Md) had significantly more deaths attributable to cardiovascular diseases (Angst et al., 2013).

This systematic review indicates that the concept of predominant polarity may have important clinical implications. First, participants with a manic predominant polarity may have a higher response rate to acute treatments for bipolar depression (Vieta et al., 2009). Furthermore, naturalistic studies suggest that BD patients with a manic predominant polarity are more likely to receive pharmacological and electroconvulsive therapy which are effective for the prevention of manic episodes (e.g., classic mood stabilizers), while patients with a depressive predominant polarity receive more frequently treatments which are effective for the prevention of depressive recurrences (e.g., lamotrigine and quetiapine) (Nivoli et al., 2013; Popovic et al., 2013b). It is

important to emphasize that a recent published guideline have suggested the integration of the concept of predominant polarity for the proper selection of available maintenance treatments for BD (Grunze et al., 2013). Importantly, Popovic et al. conceptualized the polarity index to guide the selection of treatments for the maintenance phase of BD, based on the likelihood of each approach to prevent depressive/manic recurrences (Popovic et al., 2012). A recent naturalistic study confirmed that the net polarity index of the pharmacological maintenance treatment of BD is consistent with the predominant polarity (i.e., patients with a manic predominant polarity used a maintenance treatment package with a lower net PI) (Popovic et al., 2013b). More recently this concept has been extended to encompass effective psychotherapeutic interventions for the prevention of recurrences in BD (Popovic et al., 2013a). Notwithstanding its clinical utility, concerns have been raised regarding the application of the PI to guide maintenance treatments for BD (Alphs et al., 2013). For instance, the PI may lack precision as it does not provide credible intervals. Furthermore, there are inherent limitations in using a simple proportion as an indication for treatment selection in complex illnesses, such as BD (Alphs et al., 2013).

The recently released DSM-5 did not add ‘predominant polarity’ as a course specifier for BD (Association, 2013), despite the fact that a previous ISBD Taskforce had included this parameter as a course descriptor for BD (Tohen et al., 2009). These divergent positions may reflect inherent differences in the view of descriptive (i.e., phenomenological) nosology in psychiatry. Considering that nosology should incorporate clinical phenotypes which are consistently useful for mental health care providers (McGorry, 2013), one could argue that ‘predominant polarity’ should be considered as a useful course descriptor for BD, as this systematic review demonstrates that it predicts several relevant clinical correlates of BD and may have treatment implications. However, there are no familial/genetic, neuropsychological or biomarker studies on ‘predominant polarity’ in BD. Genetic and familial studies are specially

encouraged after the recent publication of two family studies which found that mania (but not hypomania) separates from major depressive episodes in terms of familial transmission, thereby challenging the concept that mood disorders are related to a common unifying diathesis (Merikangas et al., 2013; Vandeley et al., 2013). The research domain criteria emphasizes a neuroscientific-based diagnostic system (Insel et al., 2010). At the current state of knowledge, the biological underpinnings of the predominant polarity types remain largely unknown.

One of the most important functions of systematic reviews is to identify areas where further research is necessary. This systematic review opens important areas for further research. First, the concept of predominant polarity lacks a unifying definition, and, therefore, different and alternative definitions should be tested in accordance to their predictive power. Second, there is a lack of prospective studies with large sample sizes. Therefore, more studies are necessary. Third, more studies (i.e., with larger samples) should investigate differences in the prevalence of co-occurring mental disorders and co-morbid general medical conditions as a function of the predominant polarity. Third, due to the heterogeneous definitions of predominant polarity and the distinct outcome measures reported in the included studies a meta-analysis was not performed here. Fourth, most included studies on predominant polarity come from a single research group (i.e., the Barcelona Bipolar Unit). Thus, the independent replication of the present associations by other research groups is warranted before solid conclusions can be drawn. Finally, mixed states which have been increasingly emphasized in the current nosology of affective disorders (Berk et al., 2005; Phillips and Kupfer, 2013) are not considered in the definition of predominant polarity. Future studies should address this important issue.

FIGURE LEGEND:

Fig. 1. PRISMA flowchart of studies selected for systematic review.

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Conflict of Interest

None.

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Table 1- Summary of studies included in the systematic review.

Reference No.	Country	Sample Size (N)	Design	Definition of predominant polarity	Main findings
Henry et al. (1999)	France	72 type I BD patients; DSM-IV	Cross-sectional	Percentage of lifetime manic/depressive episodes	The percentage of manic episodes was negatively associated with depressive temperament scores.
Daban et al. (2006)	Spain	300 BD patients (types I and II); DSM-III-R	Cross-sectional	Number of lifetime episodes of a given polarity higher than the number of lifetime episodes of the opposite polarity	A depressive onset of illness was significantly associated with a DPP.
Colom et al. (2006)	Spain	224 BD patients (types I and II) with a predominant polarity; DSM-III-R	Cross-sectional (consecutive enrollment)	$\geq 2/3$ of lifetime episodes of a given polarity	60.3% (n=135) had a DPP, whilst 39.7% (n=89) had a MPP. Factors associated with a DPP: BD type II, depressive onset, life-events preceding FE, substance use preceding FE, seasonal pattern, melancholia, attempted suicide, higher number of suicide attempts and more mixed episodes, higher use of lamotrigine, antidepressants and maintenance atypical antipsychotics. Factors associated with manic predominant polarity: earlier age of onset, more manic (but not hypomanic) episodes, more hospitalizations, higher acute use of atypical antipsychotics and neuroleptics.
Osher et al. (2000)	Israel	71 patients with type I BD; DSM-IV	Retrospective chart review	>50% preponderance of lifetime episodes of either polarity	55% (n=39) have illnesses characterized by more manic episodes (Md), 20% (n=20) have equal numbers of manic and depressive episodes (MD) and 17% (n=12) have predominantly depressive episodes (mD)

Table 1 (Cont.)

Reference No.	Country	Sample Size (N)	Design	Definition of predominant polarity	Main findings
Goikolea et al. (2007)	Spain	325 BD patients; criteria for seasonal pattern (SP) was recorded; DSM-IV	Prospective 10-year follow-up	$\geq 2/3$ of lifetime episodes of a given polarity	A SP was associated with a type II BD and a DPP. Following multivariable logistic regression, only the association with type II BD persisted, while the DPP did not.
Rosa et al. (2008)	Brazil	149 BD participants; 92 patients with PP included; DSM-IV-TR	Cross-sectional	$\geq 2/3$ of lifetime episodes of a given polarity	DPP was associated with years undiagnosed (NYU), was more common in BD II, and strongly associated with depressive onset. Age of illness onset was lower for DPP. Longer duration of illness and higher number of suicide attempts were associated with the DPP.
Forty et al. (2009)	UK	552 type I BD participants; ICD-10 and DSM-IV	Cross-sectional	Percentage of lifetime episodes of a given polarity $\geq 50\%$	A depressive onset of illness was associated with a DPP, while participants with a manic onset were more likely to have a MPP. On the multivariable logistic regression, DPP remained related to depressive onset of BD.
Garcia-Lopez et al. (2009)	Spain	296 BD patients; DSM-IV-TR	Prospective Follow-up time: 1-4 ys	$\geq 2/3$ of lifetime episodes of a given polarity	A predominant polarity was evidenced in 46% of the sample; 24% had DPP and 22% had MPP. At follow-up baseline predominant polarity did not predict subsyndromal affective symptoms or number of affective episode (multivariable analyses). Additional data unavailable.
Mazzarini et al. (2009)	Italy	124 type I BD patients and 19 patients with unipolar depression; DSM-IV	Cross-sectional (consecutive enrollment)	$\geq 2/3$ of lifetime episodes of a given polarity	37.9% (n=47) had a MPP and 17.7% (n=22) had a DPP. Suicidal ideation and a depressive onset of illness were associated with a DPP. No differences emerged between MPP and DPP groups regarding affective temperaments (TEMPS-A).

Table 1 (Cont.)

Reference No.	Country	Sample Size (N)	Design	Definition of predominant polarity	Main findings
Vieta et al. (2009)	Multi-centric	833 type I BD participants; 788 had	Multicenter RCT Olanzapine,	$\geq 2/3$ 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

		baseline and follow-up ratings; DSM- IV	OFC and placebo		cycling was more common in the MPP (only in men). In men a MPP was associated with a greater likelihood for treatment response.
González- Pinto et al. (2010)	Spain	169 type I BD participants; DSM-IV	Prospective	Percentage of lifetime episodes of a given polarity > 50%	30.1% (n=51) had a DPP and 26.0% (n=44) had a MPP. Baseline data: MPP group had younger age of onset and had more previous hospitalizations. DPP group had higher number of suicide attempts, more family history of affective disorders and were more frequently married. At 10-year follow-up: DPP had more episodes, more suicide attempts and more hospitalizations. At baseline there was no difference between groups in alcohol or drug abuse. At the 10-year follow-up there was a significant decrease in alcohol and other drug abuse in the MPP group
Koyuncu et al. (2010)	Turkey	216 BD participants; DSM-IV	Cross- sectional	Percentage of lifetime episodes of a given polarity > 50%	DSM-IV obsessive-compulsive disorder (OCD) did not differ according to PP.
Murru et al. (2011)	Spain	557 BD participants; DSM-IV-TR	Cross- sectional	$\geq 2/3$ of lifetime episodes of a given polarity	Prevalence of co-morbid personality disorders did not differ between MPP and DPP groups.
Nivoli et al. (2011)	Spain	604 BD participants; DSM-IV-TR	Cross- sectional	$\geq 2/3$ of lifetime episodes of a given polarity	A DPP was observed in 23.7% (n=143) and 18.9% (n=114) had a MPP. Women were significantly more likely to have a DPP.

Table 1 (Cont.)

Pachiarotti et al. (2011)	Italy	134 type I BD participants; DSM-IV-TR	Cross-sectional; consecutive enrollment	$\geq 2/3$ of lifetime episodes of a given polarity	21.1% (n=28) had a DPP and 37.3% (n=50) had a MPP. A DPP was associated with a history of pure mixed episodes (multivariable analysis).
Baldessarini et al. (2012)	Multi-centric	928 type I BD participants;	Cross-sectional	$\geq 2/3$ of lifetime episodes of a given polarity	MPP occurred in 31.3% (n=290) of the sample, while a DPP was evidenced in 21.4% (n=199) of the sample. Factors associated with a DPP: delayed diagnosis, first episode depressive or mixed, suicide attempts, ever in mixed state, ever married. Factors associated with a MPP: first episode manic/psychotic, education ≥ 12 years, family history of affective illness. Following multivariable modeling: suicidal acts and delayed diagnosis remained associated with a DPP. Two sites (US and Spain) provided information on mixed episodes. When mixed episodes were combined with depressive episodes a two-fold increase in suicidal risk was observed.
Nivoli et al. (2013)	Spain	604 BD participants (types I, II and NOS); DSM-IV	Observational	$\geq 2/3$ 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.

Table 1 (Cont.)

Reference No.	Country	Sample Size (N)	Design	Definition of predominant polarity	Main findings
Pachiarotti et al. (2013)	Italy	187 consecutive type I BD patients; DSM-IV-TR	Cross-sectional	$\geq 2/3$ of lifetime episodes of a given polarity	Principal component analysis of the brief psychiatric rating scale revealed 5 factors which explained 71.9% of the variance (psychosis, mixity, euphoric mania and inhibited depression). Mixity factor included anxiety, tension, suicidality, motor hyperactivity and excitement. In univariate analyses this factor was associated with a DPP, but significance

Popovic et al. (2013)	Spain	604 type I or II BD participants; included 257 participants with a PP; DSM-IV-TR	Observational	≥ 2/3 of lifetime episodes of a given polarity	<p>did not persist following multivariable adjustment.</p> <p>44.4% (n=114) had a MPP and 55.6% (n=143) had a DPP. Male sex, younger age, higher prevalence of type I BD, substance abuse prior to illness onset, younger age of onset, younger age at first hospitalization, higher hospitalization rate, more psychotic symptoms (lifetime and at onset) were associated with a MPP. DPP was associated with type II BD, depressive onset of illness, presence of lifetime events preceding episode, melancholia and suicide attempt rates. 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.</p>
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Notes: DPP= depressive predominant polarity; MPP=manic predominant polarity; PP= predominant polarity; BD= bipolar disorder; ICD= International Classification of Diseases; DSM= Diagnostic and Statistical Manual of Mental Disorders; FE= first episode; TCAs= Tricyclic antidepressants; SSRIs=Selective Serotonin Reuptake Inhibitors; SNRIs=Selective Norepinephrine Reuptake Inhibitors.

Table 2- Organization of the review in domains and subdomains

- a) Conceptualization and definition of predominant polarity;
- b) Prevalence rate;
- c) Socio-demographic correlates;
- d) Clinical correlates;
 - d.1) Age of onset and first episode polarity;
 - d.2) Relationships with suicidality and substance use disorders;
 - d.3) Association with co-occurring mental disorders;
 - d.4) Other clinical correlates;
- e) Treatment implications.

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Conflict of Interest

None.

Contributors

AFC, XG and KNF designed the study. AFC and KNF obtained and organized the data. AFC, DD, RSM, XG, PRN-N, DSC, TNH, MB, JA, and KNF wrote the paper. All authors approved the final version of the paper.

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Figure 1

Figure 1

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