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DISSERTATION:

PREDOMINANT POLARITY AND THE POLARITY INDEX OF DRUGS USED IN MAINTENANCE TREATMENT OF BIPOLAR DISORDER

CANDIDATE:

Dr. DINA POPOVIC

DISSERTATION ADVISORS:

PROF. GIULIO PERUGI
PROF. EDUARD VIETA

DIRECTOR:
PROF. ANTONIO LUCCACHINI

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1. INTRODUCTION

The ongoing research on bipolar disorder has highlighted its pervasive and debilitating nature, characterized by lifelong recurrent episodes and residual intraepisodic symptomatology (Keck et al., 2007). The natural history of bipolar disorder consists of distinct manic, hypomanic, depressive, and mixed mood episodes that can morph immediately from one pole to another or are separated by periods of subsyndromal symptoms and euthymia (Nierenberg et al., 2010).

Polarity, frequency, duration, and intensity of mood episodes, as well as the presence of psychotic symptoms, are highly variable. Effective treatments can decrease the frequency, duration, and intensity of mood episodes, but most people with bipolar disorder will continue to experience fluctuations in mood, as well as significant functional and neurocognitive impairment (Torrent et al.,2012; Sole et al., 2012., Nierenberg et al., 2010).

Relapse rates, even in treated patients and after a first lifetime episode, range from 40% to 60%, with nearly one-half of the patients experiencing a second mood episode within a year of recovery (Tohen et al., 2006; Tohen et al., 2003).

Inadequate treatment results in increased rates of relapse,

whereas multiple episodes may create utter vulnerability to subsequent episodes and reduce the response to therapy (Ketter et al., 2006), impact patients' psychosocial functioning (Martinez-Aran et al., 2007; Angst et al., 2002) and increase morbidity and mortality (Suppes et al., 2009).

Over the last decade, a number of effective maintenance treatments for bipolar disorder have been developed with an evidence base for second-generation antipsychotics and some anticonvulsants (Vieta et al., 2011; Fountoulakis et al., 2012), but up to date no attempt was made to develop a way to compare the drugs used in maintenance treatments of bipolar disorder according to their antidepressive *vs.* antimanic profile (Popovic et al., 2012).

The main objectives of this dissertation are:

1. To introduce a metric that would enable to compare the efficacy profiles of the drugs used for maintenance treatment of bipolar disorder as regards to their potential to prevent depressive versus manic episodes (Polarity Index)
2. To introduce Polarity Index for adjunctive psychotherapies in maintenance treatment of bipolar disorder
3. To apply Polarity Index of pharmacological treatments in

maintenance therapy to real-world setting. To perform a naturalistic study aiming to ally Polarity Index in order to assess eventual differences between predominantly manic and predominantly depressed patients, with a special focus on their pharmacological treatment.

2. BACKGROUND

2.1. Background to Bipolar Disorder

2.1.1. Historic overview

The first referral to Bipolar Disorder dates back to 3000 BC in ancient Egypt, when depression and bipolarity were mentioned in Eber's papyrus ("Book of the heart"), but are described as heart diseases and not mental disorders (Okasha and Okasha 2000).

Over time, in most societies mental illness was attributed to magical forces, malevolent deities or demons and 'treatment' was exercised by priests in the form of religious or magical rituals.

Hippocrates, Galen and Aretaeus of Cappadocia were the first to describe manic-depressive illness as a mental disorder.

Hippocrates hypothesized that yellow bile caused manic rage while black bile (which was under the influence of the planet Saturn and related to autumn) caused melancholia- which constitutes the first biological model of a mental disorder. Long-lasting anxiety, fear and moodiness were described as core characteristics of melancholia, while mania was believed to be caused by excess of blood.

Ancient Greeks described melancholia as a state of aversion to food, despondency, sleeplessness, irritability, and restlessness

and they also recognized the close relationship between depression and anxiety. Furthermore, “scientific” therapeutic interventions, such as personal hygiene, bathing and dieting, were proposed in order to “keep the humors in balance”, as well as more aggressive techniques, such as purgatives, cathartics and bleeding, were performed in “difficult-to-treat patients” or in cases of emergency in order to reset the balance of humor. Psychological treatments were also available, consisting in interpretation of dreams and talking to patients in attempt to encourage, console, and explain the illness (Plato's dialectics).

Aretaeus of Cappadocia has established a connection between melancholy and mania and described manic episodes in a very similar manner to the modern one, including the description of psychotic features and seasonality.

During the 10th and 11th century AD, the Arab scholars dominated in the field of mood disorders, while in 1621, Robert Burton wrote the first English-speaking text on the field of mood disorders the “Anatomy of Melancholy”. Later, the works of Jean-Philippe Esquirol, Benjamin Rush, Henry Maudsley, Jean-Pierre Falret and Jules Gabriel Francois Baillarger finally established the connection between depression and mania

(Fountoulakis et al., 2012).

In 1851 Falret defined bipolar disorder as an illness and coined the term "folie circulaire" (circular insanity) and in 1854 he established a link between depression and suicide. He recognized that this disorder is different from simple depression, and finally in 1875 his recorded findings were termed Manic-Depressive Psychosis, a psychiatric disorder. Another less well-known fact attributed to Falret is that he found that the disorder was more frequent in certain families, thus recognizing the existence of a genetic link (Fountoulakis, personal communication, 2012).

In 1899, Emil Kraepelin established manic-depressive illness as a distinct nosological entity and separated it from schizophrenia, on the basis of heredity, longitudinal follow-up and a supposed favourable outcome. In clinical terms, Kraepelin suggested that depression is characterized by lowered mood and physical and psychomotor retardation while on the contrary while mania is characterized by elevation and acceleration of these processes. He also described ‘involutional melancholia’ as a form of agitated mixed state. Kraepelin conceptualized three basic dimensions (fundamental symptoms) of Bipolar Disorder, concerning mood (euphoria vs. depression), cognition (flight of

ideas vs. thought slowing) and physical activity (hyperactivity vs. retardation). He proposed that these three dimensions fluctuate independently, and the different combination patterns that arise correspond to different mood episodes.

Whereas melancholia today is seen as a mood disorder, in the nineteenth century it was viewed as insanity where the patient presented with an inhibition of activity, in contrast to mania, where the patient was overactive and raving.

Esquirol introduced the notion of a mood disorder, as something quite distinct from mania and melancholia. He was the first to conceive of the possibility that a mood faculty could be disturbed separately, regardless of whatever else might be wrong with the patient.

Kraepelin's work was to grow in importance for psychiatry through the twentieth century, eclipsing first the work of Wernicke and his successors in Germany, then that of Esquirol and his successors in France, and finally that of Freud, Carl Jung, and the dynamic psychotherapists in the United States in the 1980s (Fountoulakis et al., 2012).

In terms of treatment, Bipolar Disorder is related to the earliest progress in psychopharmacology which in turn had enormous

impact not only on psychiatry but also on philosophy, ideologies and social life. In the absence of knowledge about the etiology of a condition, supplementing a study of the symptoms of a disorder with a study of its longitudinal course might lead clinicians to real disease entities (Healy, 2002).

Regarding the treatment of bipolar disorder, in 1843 Alexander Ure introduced lithium into medicine by showing that in vitro an uric acid bladder stone lost weight in a lithium carbonate solution and by the work of Sir Alfred Baring Garrod who discovered that gouty uric acids which deposit in finger joints are soluble in vitro in a lithium solution. On these bases, Armand Trousseau and Alexander Haig have suggested that mania and depression may be related to the uric acid nosology.

As a matter of fact, modern psychopharmacology commenced with the use of lithium for the prophylaxis of recurrent depression by Karl Georg Lange in 1886, for acute depression and milder bipolar cases by Frederik Lange in 1894 in Denmark, and for the treatment of mania by William Alexander Hammond in the US.

From the late 1880, lithium was available in the form of therapeutic mineral spring waters and lithium tablets. Cases of

severe intoxications by lithium emerged, resulting in cases of deaths, and in 1949 lithium products were removed from the market.

After the World War II, John Cade injected urine from patients to guinea pigs to test the hypothesis that mania is caused by intoxication by a normal body element circulating in excess, whilst melancholia would be determined by its reduction. The guinea pigs would appear to die faster than when healthy persons' urine was used, leading him to think that perhaps more uric acid was present in the samples provided by his mentally ill patients. Then, in an effort to increase the water solubility of uric acid, lithium urate was added to the solution. Cade found that in the guinea pigs injected with the lithium urate solution, toxicity was greatly reduced. However, the control group in his experiments revealed that the lithium ion had a calming effect by itself. After ingesting lithium himself to ensure its safety in humans, Cade began a small-scale trial of lithium citrate and/or lithium carbonate on some of his patients diagnosed with mania, dementia præcox or melancholia, with outstanding results. The calming effect was so robust that Cade speculated that mania was caused by a deficiency in lithium.

In 1949 Cade reported positive results in 10 manic patients (Cade 1949), however two years later he reported the first death because of lithium toxicity in a patient whose bipolar illness otherwise responded extremely well to treatment. Toxicity of lithium, that lead to several deaths (before the suitable tests to measure the lithium level in the blood were developed), alongside with the fact that lithium is a naturally-occurring chemical, thus lithium salt could not be patented, meaning that its manufacturing and sales were not considered commercially viable, lead to abandon lithium use for the second time. In fact, hese factors prevented its widespread adoption in psychiatry for some years, particularly in the United States, where its use was banned until 1970.

In the 1960s the first double blind trial in psychiatry, involving lithium, was conducted by Mogens Schou (Schou et al. 1954). Sharp criticism and reservation followed this publication and many prominent psychiatrists questioned lithium's effectiveness and emphasized its toxicity (Blackwell and Shepherd 1968; Shepherd 1970; Blackwell 1969, 1970, 1971, 1972). Only during the 1970s and after subsequent work by Paul Baastrup (Baastrup 1964; Baastrup et al. 1970; Baastrup and Schou 1967) lithium

was established in the treatment of bipolar disorder (Bech 2006; Schioldann 1999, 2011; Schioldann 2006).

Following the success with lithium treatment, valproate was introduced in 1966 (Lambert et al. 1966) followed by carbamazepine (Okuma et al. 1979). Antipsychotics were introduced by Delay and Deniker in 1955 and among the patients they treated probably many were bipolar patients with acute mania (Delay and Deniker 1955). Second generation antipsychotics were introduced and became widely accepted from 2000, mostly due to their tolerability, in particular for the low incidence of tardive dyskinesia. Benzodiazepines were introduced by Sternbach in 1956. In 1958 Roland Kuhn reported on the efficacy of the first antidepressant, imipramine (Kuhn, 1958).

There were several reports in the 1970s suggesting that the use of antidepressants might induce mania, mixed episodes and rapid cycling. In 1994 American Psychiatric Association published the first operational treatment guidelines. Also, during this period the first meta-analytic studies emerged, and the Evidence-Based Medicine principles gained ground in the treatment recommendations (Fountoulakis, 2012, personal communication).

2.1.2. Epidemiology and Course of illness

Bipolar disorder (BD) is a chronic mood disorder affecting around 4% of adults (Merinkagas et al., 2007) with a prevalence ranging from 1% (bipolar disorder type I) to 6.5% (bipolar spectrum disorders, including bipolar I and II disorders) in the general population (Vieta et al., 1997; Hirschfeld and Vornik, 2004; Merikangas et al., 2007). Bipolar disorder is a severe, chronic and recurrent disorder with a high prevalence of subsyndromal interepisodic symptomatology (De Dios et al, 2012; Bonnin et al., 2012) and a significant impairment in the affected individuals (Sanchez-Moreno et al., 2009; Rosa et al., 2011).

Bipolar disorder is recognized as one of the world's 10 greatest public health problems (Murray and Lopez, 1997). Patients with bipolar I and II disorder spend half of their lifetime in a symptomatic state and almost all patients encounter high rates of affective recurrences (Dittmann et al., 2002, Joffe et al., 2004, Post et al., 2003). Despite the dramatic and life-disrupting nature of mania, some studies have documented that depressive episodes, rather than the manic ones, have the strongest impact on quality of life and functional outcome (Judd et al., 2005; Depp

et al., 2006; Post, 2005; Hirschfeld, 2004).

In studies that recruited only bipolar I patients, a depressive index phase predicts longer time needed to full remission, utter acute episodes, more time spent in any mood episode, and lower percentage of patients reaching full symptomatic and functional remission (Post, 2003; Nolen, 2004; Tohen, 2003). Patients with depressive symptoms have a higher suicidal rate and more suicidal behaviour (Valtonen et al., 2006; Galfalvy et al., 2006). Moreover, depressive symptoms are responsible for an increased risk of somatic illnesses, such as obesity and cardiovascular disease, therefore reducing overall life expectancy (Disease et al., 1997; Fagiolini et al., 2002; Mitchell and Malhi, 2004).

Two of the reasons for the improvement of prognosis in this population are the steady and substantial decrease of misdiagnosis of bipolar type I disorder as schizophrenia or unipolar depression, as well as the fact that the most recent classification systems, DSM-IV-TR and ICD-10 have made the diagnosis of manic-depressive disorders more inclusive. The further subdivision of bipolar mood disorders into bipolar I (depression with a history of mania or mixed episode) and bipolar II (depression with history of hypomania, but not with

mania) was proposed almost 30 years ago (APA, 1994, WHO, 1991). Since then, several studies have demonstrated that bipolar II disorder represents a quite common, clinically and biologically distinct form of affective disorders that should be differentiated from both bipolar I disorder and unipolar major depressive disorder (Akiskal and Mallya, 1987) and that it leads to similar, sometimes even worse, psychiatric and social consequences than bipolar I and unipolar patients.

2.1.3. Clinical characteristics and diagnosis

The diagnosis of bipolar disorders is based on clinical criteria which are hence subject to controversy and interpretation. Nonetheless, bipolar disorders (especially type I) have a greater validity of construct and long-term stability than those of other mental disorders. The manic states are typically characterized by elated mood, increment in quantity and speed of speech, quicker thought, increased psychophysical activity, greater energy (with a corresponding decrease of need to sleep), irritability, perceptual acuity, paranoia, hypersexuality and increased impulsivity. The degree of type and duration of these cognitive, perceptual, behavioural and neurovegetative alterations determine the distinction between hypomania and mania. In hypomania, the abovementioned changes are generally moderate and may or may not result in serious problems for the individual experiencing them, and may even determine increased productivity and are often seen as egosyntonic and subjectively pleasant. In more intense episodes, however, they can disrupt the lives of the patients, their families, and social functioning. Hypomania is a very labile condition which often evolves into full-blown mania or is followed by depression, also facilitated by increased alcohol

and substance misuse during the episodes.

The bipolar depressive states, in sharp contrast to the manias, are usually characterized by a slowing or decrease in almost all aspects: rate of thought and speech, energy, sexuality, and the ability to experience pleasure or sometimes even emotions. The depressive phase of bipolar disorder is often accompanied by apathy predominating over sadness, psychomotor inhibition over anxiety, hyperphagia rather than hyporexia, hypersomnia over insomnia.

According to DSM-IV-TR, mixed episodes are defined as the co-existence of both depressive and manic symptoms to the extent the criteria for both a manic and a depressed episode are fulfilled, while in contrast the ICD- 10 definition considers it as either a mixture or a rapid alternation (i.e. within a few hours) of hypomanic, manic and depressive symptoms. In real-life clinical setting, most patients present a mixture of a number of manic and depressive symptoms in a combination which does not fulfil the DSM criteria for a manic, depressive or mixed episode, and thus could be diagnosed in the cathegory of not-otherwise-specified (NOS) mood episode (Fountoulakis et al., 2012).

As abovementioned, according to formal classification, bipolar

disorder consists of at least one manic (Bipolar Disorder I), hypomanic (Bipolar Disorder II) or mixed episode and a depressive episode.

The term “rapid cycling” refers to patients suffering from at least 4 mood episodes in a year. It seems more frequent in female patients and in higher social class subjects (Fountoulakis et al., 2012).

Psychotic features are common in bipolar patients and may include delusions or hallucinations of any type, and they can be mood-congruent or even non-congruent, and both could occur in the context of any type of episode. In fact, the diagnostic criteria for schizoaffective disorder according to DSM-IV-TR require the presence of a psychotic episode in the absence of prominent mood symptoms.

BD also presents significant rate of psychiatric comorbidity, according to most studies with a prevalence of 50% -70% (Vieta et al., 2001) or even higher. The presence of comorbidities is associated with worse prognosis, more severe subtypes, earlier onset, lower remission rates, suicidal behaviour, lower response to treatment, worse functioning and quality of life (Vieta et al., 2012; Pacchiarotti et al., 2009: Vieta et al., 2001; Nery-Fernandes

et al., 2009). The most common psychiatric comorbities of bipolar disorder are represented by anxiety and substance abuse disorders (Vieta et al., 2012).

Alcohol abuse could be present in more than half of the patients and frequently represents self-medication efforts. The drug abuse pattern of bipolar patients concerns mainly stimulants (Winokur et al., 1998). Cognitive impairment is reported to exist in both Bipolar I and Bipolar II patients, with a higher frequency among bipolar I patients, and it is present in all phases of the disorder, even during euthymia (Sole et al., 2011, Malhi et al., 2004). Various studies suggest that there is a significant degree of psychosocial impairment even when patients are euthymic and report that only a minority achieves complete functional recovery (Daban et al., 2006; Mur et al., 2004).

The correct diagnosis is frequently made only after several years from the onset, since the first episode is often depressive and the correct diagnosis is made only after a manic or mixed episode emerges. More than half of the patients with depressive onset will be diagnosed as bipolars within the following 20 years (Angst et al., 2005), indicating the misdiagnosis of the first episode(s) as unipolar depression.

A number of illness features have been proposed to indicate risk of bipolar disorder in the context of a depressive episode, including earlier age of illness onset, greater number of depressive recurrences or briefer episodes, family history of bipolar disorder and aspects of temperament such as hyperthymia and cyclothymia. Regarding the symptoms, indicators of bipolarity are presence of irritability or anger, presence of psychotic symptoms, suicidality, and atypical neurovegetative symptoms including psychomotor agitation or slowing. Moreover, even in individuals who do not meet full syndromal criteria for bipolar I or II disorder, it has been suggested that these illness features may be markers for an underlying bipolar diathesis or bipolar spectrum illness (Perlis et al., 2011). This goes much beyond academic interest, with profound implications for the treatment and its overall efficacy. An additional problem for the diagnosis is that patients usually experience hypomania as a recovery from depression, often a pleasant egosyntonic mood state, which may pass unobserved by the clinicians and unreported by the patient himself.

2.1.5. The clinical implications of cognitive impairment and allostatic load in bipolar disorder

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Review

The clinical implications of cognitive impairment and allostatic load in bipolar disorder

E. Vieta [a,*], D. Popovic [a,b], A.R. Rosa [a,c], B. Solé [a], I. Grande [a], B.N. Frey [d], A. Martinez-Aran [a], J. Sanchez-Moreno [a], V. Balanzá-Martínez [e], R. Tabarés-Seisdedos [e], F. Kapczinski [c]

[a] Bipolar Disorders Program, Clinical Institute of Neuroscience, University Clinic Hospital of Barcelona, IDIBAPS, CIBERSAM, Villarroel 170, 08036 Barcelona, Spain
[b] Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Ospedale Santa Chiara, Via Roma 67, 56100 Pisa, Italy
[c] Bipolar Disorders Program and INCT for Translational Medicine, Hospital de Clínicas de Porto Alegre, UFRGS, Ramiro Barcelos, 2350 CEP 90035-003, Porto Alegre, RS, Brazil
[d] Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada H3A 2B4 and Montreal Neurological Institute, McGill University, Montreal, QC, Canada
[e] Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, CIBERSAM, Blasco-Ibáñez 17, 46010 Valencia, Spain

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ABSTRACT

Background: Allostatic load (AL) relates to the neural and bodily "wear and tear" that emerge in the context of chronic stress. This paper aims to provide clinicians with a comprehensive overview of the role of AL in patophysiology of bipolar disorder (BD) and its practical implications.
Methods: PubMed searches were conducted on English-language articles published from 1970 to June 2011 using the search terms allostatic load, oxidative stress, staging, and bipolar disorder cross-referenced with cognitive impairment, comorbidity, mediators, prevention.
Results: Progressive neural and physical dysfunction consequent to mood episodes in BD can be construed as a cumulative state of AL. The concept of AL can help to reconcile cognitive impairment and increased rates of clinical comorbidities that occur over the course of cumulative BD episodes.
Conclusions: Data on transduction of psychosocial stress into the neurobiology of mood episodes converges to the concept of AL. Mood episodes prevention would not only alleviate emotional suffering, but also arrest the cycle of AL, cognitive decline, physical morbidities and, eventually, related mortality. These objectives can be achieved by focusing on effective prophylaxis from the first stages of the disorder, providing mood-stabilizing agents and standardized psychoeducation and, potentially, addressing cognitive deficits by the means of specific medication and neuropsychological interventions.

1. Introduction

The term "allostatic load" was introduced by McEwen and Stellar [86] to refer to a cumulative, multisystem view of the physiologic toll that is required for adaptation to stress. Although adaptive mechanisms of allostasis can be protective for the individual, there is a price to pay for this forced re-setting of parameters, especially if allostatic processes become extreme or inefficient. The cost of these processes is called *allostatic load*. In other words, it is the "wear and tear" on the body and brain resulting from chronic over-activity or inactivity of physiological systems that are involved in adaptation to environmental challenges [87]. The effects of allostatic load (AL) are cumulative and most notably seen during the process of aging and chronic stress. Subjects with highest AL were found to have increased risk for incident cardiovascular disease, physical and cognitive decline, and all-cause mortality in cross-sectional and follow-up studies [57,56,58,135,134,133].

Neurocognition has been the focus of extensive research in schizophrenia and, more recently, in bipolar disorder (BD) [29,39,73,76,115,129]. Neuropsychological testing may represent a tool able to identify potential neuroimaging markers and endophenotypes [23,46,124,149] and to better understand the underlying neurophysiology [49]. However, only lately the highly consistent findings from research began to be applied to clinical practice, and many clinicians are not much aware of how neurocognitive deficits affect their patients' daily life, and, importantly, what can be done to prevent or at least mitigate cognitive impairment. Recent evidence suggests that neurocognitive status may be the most powerful predictor of functional outcome in BD, even more so than clinical features [80].

Bipolarity, as a severe form of mood disorder, cognitive impairment, and increased physical morbidity and mortality, converge in the concept of *allostatic load*.

The present paper deals with the most recent findings connecting cognition, physical health, comorbidity and functional outcome in BD. Particular emphasis is made on what the clinician

* Corresponding author. Tel.: +34 93 2275401; fax: +34 932275795.
E-mail addresses: evieta@clinic.ub.es, jose.sanchez.moreno@cibersam.es (E. Vieta).

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can do to prevent or possibly reverse the detrimental effects of AL and its impact on patients' lives.

A PubMed search of the literature, using search terms "allostatic load" and "bipolar disorder" cross-referenced with "cognitive impairment", "comorbidity", "mediators", and "prevention", was performed. The search was supplemented by manually reviewing reference lists from the identified publications. Only English-language articles published from 1970 to July 2011 were included. The results of this search are presented in this article and examined under the light of a unifying hypothesis, together with some suggestions for further research in this intriguing area.

2. Allostatic load and its mediators

The concept of AL may help to integrate apparently unrelated findings among bipolar patients such as vulnerability to stress, cognitive impairment and higher rates of physical comorbidity and mortality [53]. BD can be hypothesized as a disease of cumulative allostatic states where AL increases progressively as mood episodes occur over time. The mediators of AL include genes [27], neurotrophic factors [128], neurotransmitters [83], hormones [160], immune-inflammatory system [156] and oxidative stress [15]. Hence, although essentially related to normal function and protection of the brain, the mediators of allostasis are also associated with increased risk of systemic damage and neuron cell endangerment, when excessive [144]. All organs are subject to the deleterious effects of AL, but the brain tissue appears to be particularly vulnerable [131]. On the other hand, brain also exerts an integrative role in the process of stress response, as it orchestrates the action of several adaptive systems such as cardiovascular, metabolic and immune systems through a series of primary mediators, such as adrenal steroids, catecholamines, dyhidroepiandrosterone (DHEA), prolactin, thyroid and growth hormones, cytokines and neurotransmitters (Fig. 1). These mediators influence cellular events through their action in receptors, enzymes, second messenger systems and gene expression. The paradoxical role of the brain in triggering allostatic processes and being vulnerable to its effects provides a suitable model for cognitive decline in the context of neurodegenerative disorders. It is plausible that a cycle of higher vulnerability of BD patients and greater AL may account for the clinical decline and poor outcomes described in more severe forms of bipolar illness.

The structural and functional changes in the brain associated with aging and the cognitive decline associated with chronic elevated levels of glucocorticoids provide evidence of the long-term burden caused by AL [83]. Adaptive plasticity is seen in response to acute and chronic stress, as indicated by synaptic and dendritic remodeling, neurogenesis, and atrophy of neural structures, particularly in the hippocampus [36,82]. Repeated stress is also related to decreased neurogenesis in the dentate gyrus, and chronic administration of various classes of drugs increases the neurogenesis in the dentate gyrus and hippocampal hilus in rats [71]. Although essential to normal synaptic neurotransmission, stress-induced dysfunctional activity of neurotransmitter systems can lead to excessive formation of free radicals that can damage neural cells [83]. Glucocorticoids and mediators of allostasis interact with neurotransmitter systems and brain peptides resulting in neuroplastic alterations seen in hippocampus, amygdala and prefrontal cortex [85]. In addition to the critical role of glucocorticoids in the hippocampus, AL is also responsible for important alterations in other brain structures. Chronic stress in animal models is related to abnormal neuronal

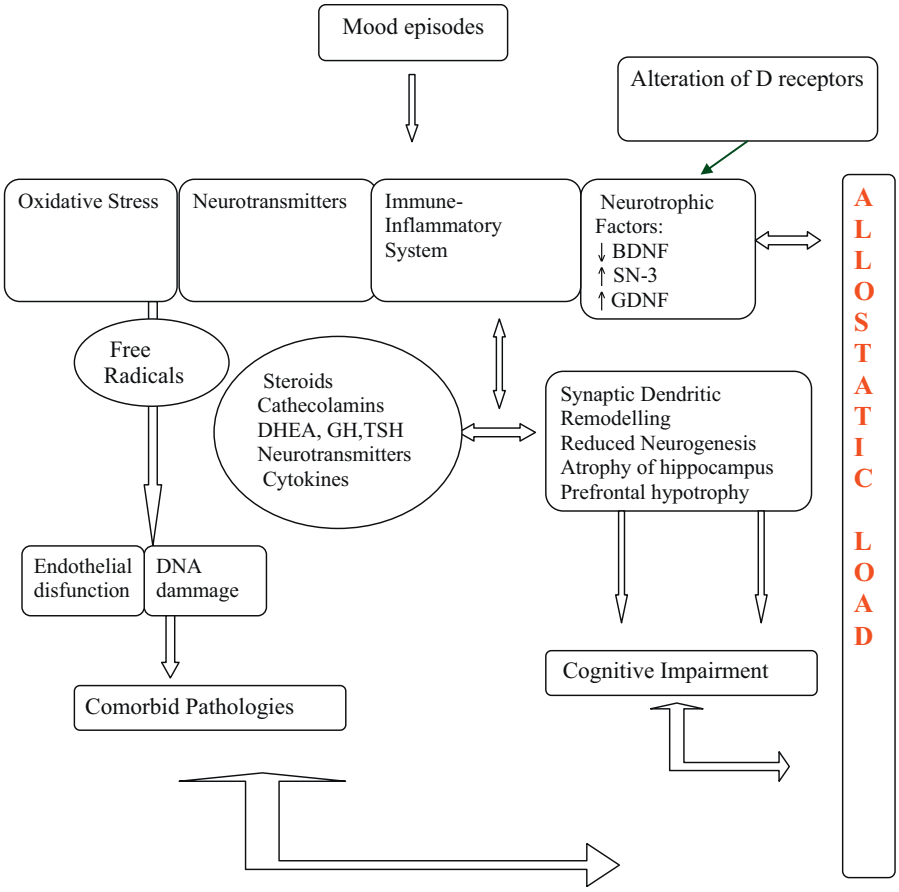

Fig. 1. Allostatic load correlates.

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remodeling in the prefrontal cortex [21,51,75,95], particularly in glial cells [34], and amygdala [165,164]. Structural and functional magnetic resonance imaging studies in depression and Cushing's disease, as well as in anxiety disorders, provide evidence that the human brain may be similarly affected [85]. If higher AL is associated with higher mortality, morbidity and cognitive impairment, identifying and addressing clinical biomarkers of AL can have important biomedical implications [52].

Oxidative stress is one of the main mediators of AL. Recent studies have reported alterations of biological markers of oxidative stress in BD patients. Serum TBARS (thiobarbituric acid reactive substances) levels were increased in all phases of BD, while calcium binding protein B (S100B), associated to brain damage, increments in mania and depression, but not during euthymia. The damage seems to be more evident in mania [4]. Alteration in intracellular signaling pathways within the mitochondria may be associated with cell apoptosis in response to oxidative stress [14]. Oxidative stress plays a key role in the induction of DNA damage, endothelial dysfunction and telomere shortening [53]. BD outpatients present an increased frequency of DNA damage when compared to controls [5]. The frequency of DNA damage correlates with the severity of symptoms of depression and mania. Both depressed and euthymic bipolar patients present impairment of endothelial function due to oxidative stress, which may increase risk for cardiovascular conditions [125]. Oxidative stress is also implicated in accelerated telomere shortening [127]. Accelerated telomere shortening was also detected in individuals with BD. Taken together, these studies suggest that chronic oxidative stress associated with mood disorders may contribute to excess vulnerability for aging-correlated diseases such as cardiovascular pathology [138].

Another potential source of oxidative stress in BD is dopaminergic system alteration during manic episodes [15] and distorted homeostasis of dopamine receptor subtypes in bipolar patients [107,163]. Treatment with antipsychotic medication is associated with a downregulation of D1 receptor expression [68] and increase of D3 receptors [163]. Signal transduction pathways activated by oxidative stress have been implicated in mood disorders and in several chronic medical disorders such as obesity, diabetes and cardiovascular disease [90].

Some of the changes in brain morphology described to be associated with AL have also been reported in patients with BD. It is noteworthy that some growth factors, which are altered by stress, have been also shown to be changed in BD. This is particularly true in the case of a particular protein involved with neuroplasticity and neurogenesis, the brain-derived neurotrophic factor (BDNF) [113]. It has been recently demonstrated that serum BDNF levels decrease during both manic and depressive episodes. Moreover, BDNF levels were negatively correlated with severity of manic and depressive symptoms [33,69]. In addition, a single polymorphism of the BDNF gene (Val66Met) has been associated with impaired cognitive performance [123] and increased risk to rapid cycling [48,97] in BD patients. Euthymic patients (both val/val and met carriers for the BDNF gene) had similar serum BDNF levels in comparison to controls, suggesting that the normalization of BDNF levels may be associated with mood stability [155]. Serum neurotrophin-3 and glial cell line-derived neurotrophic factor levels, though, are increased during acute mood episodes [120,166], which may indicate a compensatory response to BDNF decrease. Some of the brain structural changes that have been described in BD, such as enlargement of amygdala and reduction in the size of prefrontal cortex and hippocampus [11,18,96], may in fact reflect enduring malfunction patterns of circuits involved in conferring the emotional valence of experiences [111]. If the gate system to code experiences as stressful is overactive and defective, such malfunctioning would render bipolar patients more vulnerable to stress and its neurobiological consequences, therefore increasing susceptibility to trigger AL.

3. Cognitive impairment in bipolar disorder

There is indisputable evidence that BD is associated with significant neurocognitive deficits across all mood states [78]. Cognitive deficits persist during euthymia and may include attention, executive function and verbal memory impairment [77,98,119]. These cognitive dysfunctions may reflect abnormal activation patterns in the brain [13,142], implicating the prefrontal cortex in the etiopathogenesis of bipolar illness and positing cortical-subcortical-limbic disruption as the underlying cause [72,104]. Such deficits do not seem to be specific and their pattern is quite similar to schizophrenia, albeit overall less severe [35]. Euthymic bipolar patients demonstrate relatively marked impairment in executive function and verbal memory [119]. It is not clear yet whether these are two discrete areas of impairment or are inter-related. In addition, is yet to be determined whether neuropsychological impairment is present in premorbid state, although several studies suggest that bipolar patients may be relatively preserved from the neurocognitive point of view before developing their condition [67]. Several studies have assessed cognitive performance of large cohorts of children or youth and analyzed the specific profile of those who would subsequently develop BD or schizophrenia; overall, there is no suggestion for severe premorbid deficits, whereas there seems to be so for schizophrenia [25,117,170] perhaps with the exception of visuospatial reasoning [152]. Interestingly, subjects at risk for BD were more likely than subjects at risk for schizophrenia and even than subjects at no risk for mental disorders to perform better in some domains [25], particularly at arithmetic reasoning [152]. Neuropsychological studies on first-degree relatives of subjects with BD, though, suggest that there might be some mild deficits underlying vulnerability to the disorder in the areas of psychomotor speed and executive function [7,9,147], but not verbal memory [30]. In fact, verbal memory was not found to be related to increased risk for BD in premorbid neuropsychological studies [152], but seems to be strongly affected by the impact of multiple episodes [77], subthreshold depressive symptoms [92], and medication [19,79]. Hence, verbal memory may be a potential treatment target by means of effective prophylactic treatment, improvement of subclinical depressive symptoms, and rational use of medication. Importantly, verbal memory performance has been reported to be highly correlated with functional outcome [3,80].

Neurocognitive impairment may not occur exclusively in individuals with BD I, as it has also been reported in BD II [153], schizoaffective disorder bipolar type [154], bipolar patients with and without history of psychosis [19,81,136], bipolar suicide attempters [50], bipolar patients with comorbid conditions [122,157], and pediatric BD [109]. On the other hand, a subset of bipolar patients seems to have little or no cognitive impairment [2]. Thus, the study of bipolar subtypes and subgroups, including those who do not show cognitive deficits, may provide important clues for the effective treatment and prevention of cognitive impairment and psychosocial dysfunction.

The number of longitudinal studies on the course and outcome of cognitive dysfunctions in BD is very limited. Although there is evidence that multiple episodes carry more cognitive impairment [10,61], in particular the manic episodes [78], only a few studies have addressed this issue in a prospective, longitudinal design. Neuroimaging studies are also mostly cross-sectional, although there is evidence that patients with multiple episodes, and especially more manic episodes, are more likely to have enlarged ventricles and gray matter atrophy than first-episode patients [141]. Data from the few longitudinal studies available suggest

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that, even with mood-stabilizing effective treatment, deficits improve little over time [8,41,88,99,150], but they do not seem to lead to any sort of dementia-like syndrome [38].

Neurocognitive symptoms are not only important because they tell us about the brain areas and functions involved in the pathogenesis of the disease and represent potential endophenotypes, but also for their clinical value; there is an ongoing debate on to what extent they should be included in the diagnostic criteria for schizophrenia [60] and BD [158]. Interestingly, there is no perfect match between cognitive impairment as reported by the patients and as assessed with neuropsychological tools [22,79]. Subjective cognitive impairment may be more closely related to enduring subthreshold depressive symptoms and/or medication side-effects [79,162] than objective impairment, which would be associated to the endotoxic effects of mood episodes and AL [53]. This sort of "true" cognitive dysfunction would be close to the concept of anosognosia [44] and the type of deficits that can be seen in neurodegenerative conditions.

Medication may play an important role in the etiology and also in the treatment of cognitive problems. Most studies are unable to disentangle the potential effects of medication on cognition, because patients are usually medicated. Extrapyramidal, anticholinergic, anticonvulsant, and sedative effects of medications may affect some of the cognitive functions. There have been claims that some medications might improve cognition in psychosis, but the results were confounded by parallel clinical improvement. There is little, if any, evidence that medication by itself may help to improve cognition. Studies in healthy volunteers have evidenced that lithium therapy is associated with small but significant impairment in immediate verbal learning, memory and creativity [168]. Both lithium and valproate decrease blood-oxygen-level-dependent (BOLD) signal magnitude during various tasks in distinct brain regions in healthy volunteers [12]. Studies in non-medicated bipolar subjects exist [151], but they are difficult and often confounded by severity bias, as non-medicated patients tend to be less severe than those who cannot discontinue treatment. Although some medications might have a better profile regarding cognitive side-effects, there is little evidence to support this claim so far for any specific compound [42]. The area of potential therapies, both pharmacological and psychosocial, particularly targeted to improve cognitive dysfunctions, will surely quickly develop in near future [24,159].

Whatsoever, structural abnormalities were reported to be present in bipolar children and adolescents [110] suggesting that these are not due to the effects medication or multiple mood episodes.

Finally, cognitive dysfunction may also be influenced by psychosocial factors, such as inability to fulfill academic achievements, decreased reading time and cultural interests, and decades ago, by institutionalization. Most studies try to search for these factors, and it is still unclear whether they can actually help, if reversed, to remediate some cognitive deficits [108].

4. Staging

As previous studies have shown, alongside with decrease in BDNF levels during mood episodes [33,137], multiple episodes may impair the restoration of the levels of BDNF [59]. This finding is in agreement with the evidence of better clinical outcome for patients at early stages of illness [130], better treatment response, especially to lithium [145] and olanzapine [63], longer duration of euthymia in interepisodic periods [62]. Based on these observations, a staging model was proposed by Berk et al., [15] and elaborated by Kapczinski et al. [55].

Berk et al. [15] highlighted the need to define clinical features and differentiate treatment strategies according to stages. The progression of BD is staged according to the spectrum that presents prodromal stages at one end, and refractory clinical presentations, which could culminate with persistence of unremitting illness on the other end. The progression is facilitated by the cumulative exposure to acute episodes, substance abuse, life stress summed with inherited vulnerability [53]. The failure of compensatory mechanisms following the exposure to environmental stressors and the subsequent cumulative mood episode-related toxicity may account for lower life expectancy in bipolar patients [55,102]. The staging model has important clinical implications, proposing early intervention and neuroprotective strategies in early phases, while the latter stages may require more rehabilitative interventions. Recently, Kapsczinski et al., [54] have suggested the need to include neurobiological parameters/biomarkers, assessment of neurocognition, psychosocial functioning and autonomy alongside the longitudinal evaluation of clinical variables. This approach will utterly facilitate a better understanding of the mechanisms underlying progression of BD and ameliorate treatment strategies.

5. Prevention and treatment of cognitive and allostatic load correlates in bipolar disorder

The implication of AL in provides the grounds for further hypothesis of its role in determining cognitive impairment [78], medical [26], and psychiatric comorbidity [93,161].

5.1. Allostatic load correlates: medical comorbidity

BD is highly comorbid with a wide range of medical disorders, such as cardiovascular, metabolic, infectious, neurological and respiratory [26]. According to many studies, BD is associated with higher rates of mortality for all natural causes except cancer [26]. The lack of increased oncological risk may be secondary to potential anti-cancer properties of mood stabilizers as well as other mediators of negative comorbidity [148]. Valproate has an antiproliferative and differentiating effect in vitro and in vivo, with potential oncological benefits [139]. Recent *in vitro* studies have evidenced antiproliferative action of lithium as well [105,143].

AL may play a role in physical and cognitive decline, cardiovascular disorders [133], immunity impairment, obesity, bone demineralization and atrophy of cerebral nerve cells [84], whose association with BD is well established. There is evidence that reduction in AL is associated with lower all-cause mortality, even in geriatric patients [58], and should therefore represent a treatment target in all age groups.

Drugs implied in treatment of BD also play a role in medical comorbidity. Second-generation antipsychotics are associated with increased risk of weight gain, diabetes mellitus and cardiovascular disease [89,101]. On the other hand, mood stabilizers [6,43,69] and SSRIs, often prescribed in adjunction to mood stabilizers in bipolar depression, can diminish AL secondary to depressive episodes as well as oxidative stress [64,169] and therefore may decrease medical comorbidity, especially in Bipolar II disorder [90], although the evidence supporting their efficacy in that condition is still very weak.

5.2. Allostatic load correlates: psychiatric comorbidity

BD also presents significant rate of psychiatric comorbidity. Most studies report prevalence between 50% and 70% [161] or higher [93] with one recent study reporting lower lifetime prevalence of 27.4% in euthymic patients [100]. The presence of comorbidities is associated with worse prognosis, more severe

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subtypes, earlier onset, lower remission rates, suicidal behaviour, lower response to treatment, worse functioning and quality of life [91,100,161]. Most frequent comorbidities are represented by substance use disorders and anxiety disorders [93]. A growing body of evidence indicates that some of the neuroadaptive changes that occur in "brain stress systems" in patients with addiction [66] are comparable to those described as associated with AL. Therefore we suggest that substance abuse should be seen as a mediator of AL. In fact, Maremmani et al., [74] have proposed that bipolar spectrum disorders and addiction should be considered under a unitary perspective as they often co-occur and constitute reciprocal risk factors while stressing the need to combine opiate agonists with mood-stabilizing therapy. Pacchiarotti et al., [106] have hypothesized the existence of a subtype of BD in which substance misuse may trigger, and perhaps maintain, mood symptoms in vulnerable individuals. These individuals would benefit from primary prevention programs as well as psychoeducational strategies [31] combined with pharmacotherapy.

5.3. Cognitive impairment

Patients with BD frequently display subthreshold symptoms [62] and cognitive impairment [78] during all phases of BD. The persistence of cognitive function impairment contributes, alongside multiple mood episodes, to exacerbate AL [53]. Cognitive impairment, especially verbal memory function, predicts reduced psychosocial functioning [80] and represents a potential target of prophylactic treatment.

Neurotrophins and inflammatory cytokines such as TNF-α can be considered as neurobiological markers implicated in neurodegeneration and cognitive impairment in BD [37,65]. BDNF and lithium, through the phosphatidylinositol pathway are able to neutralize glutamate-stimulating effects of TNF-α and other inflammatory mediators [1,59]. Several studies have pointed out that mechanism of action of mood-stabilizing medication may include cyclooxygenase2 (COX-2) inhibition and reduction in inflammatory cytokines [20,45,116]. As previously mentioned, it has been demonstrated that chronic treatment with lithium and valproate can inhibit oxidative damage [6,43,69] and thus may play a role in preventing cognitive impairment due to AL. Recent evidence suggests that lithium determines a decrease in pro-inflammatory mediators in BD, but not among non BD subjects [47]. Another pathway by which lithium may provide enhancement of learning and memory [103,167] might include stimulation of BDNF, reported as reduced during manic and depressive episodes [33,69], bcl-2 production, and inhibition of GSK-3beta [121,126]. Since BDNF expression is altered in BD and under stress, we can speculate that lithium, through enhancement of BDNF, is able to diminish AL correlates in BD.

Family intervention, CBT, group psychoeducation, interpersonal social rhythm therapy have shown good prophylactic efficacy when combined with pharmacotherapy in BD [94]. Psychoeducation for caregivers has also shown to improve illness outcome, especially in the early stages [118].

5.4. Multiple episode cumulative damage

In order to characterize changes in the cognitive-affective evolution over time in BD and its progression from prodromal phase to a clear-cut clinical disorder, and at times to a resistant condition, various models have been proposed [140]. These include neurosensitization [114], staging and AL theories.

In the early 1990s, Post has put forward the "kindling theory" according to which biochemical and anatomical substrates underlying the affective disorders evolve over time as a function of recurrences, favouring new episodes on one hand and reducing pharmacological responsivity on the other [112].

In BD, the cumulative damage from persistent AL probably sums up to kindling and sensitization mechanisms deriving from multiple recurrences [53]. Patients with more previous mood episodes were reported to present higher comorbidity rates, especially substance abuse, poorer social adjustment, increased risk of hospitalization, suicide rates and forensic complications [17]. Similar trend was detected also among children and adolescents with BD- those with multiple episodes per year presented a higher comorbidity, in particular Attention Deficit Disorder, and required more hospitalizations and pharmacological treatment than those without multiple episodes [28].

Recurrent episodes may influence the outcome by creating utter vulnerability to subsequent episodes as well as by reducing the response to therapy [63]. In addition, response to lithium is inversely correlated to number of episodes [145] and duration of illness prior to starting treatment [70]. Consistently, olanzapine was found more effective early in the course of BD [63]. The same is true for psychotherapy; patients with multiple recurrences do not seem to respond to adjunctive cognitive-behavioural therapy [132]. Similarly, the number of previous episodes clearly appears to reduce the response to psychoeducation, although perhaps in a more subtle way than that observed in cognitive-behavioural therapy [32].

In a recent study [17] have evidenced that both response to treatment rates and relapse rates were more favourable in patients with fewer mood episodes, the best being for patients with one to five lifelong episodes, followed by the group with five to ten episodes, the least favourable being for patients with more than ten episodes.

Together, these results suggest that neuroplastic changes associated with the progression of illness can negatively affect treatment success.

6. Limitations and conclusions

While there is evidence of structural abnormalities in bipolar disorder, indicating dysfunction in subcortical (striatal-talamic) and limbic regions, observable early in the course of the illness which suggests that they are not merely the sequelae of recurrent affective episodes or pharmacotherapy, and a growing understanding of the molecular mechanisms that may underpin these abnormalities [140], the psychobiological models still present various gaps. Defining biomarkers according to stages of bipolar disorder, still largely lacking, would be useful to ameliorate diagnostic validity and clinical utility of the proposed models. It is not yet clear to which extent it is possible to reverse the progression of bipolar disorder, whether a Stage 4 patient can go back to Stage 3, or even 2. Nevertheless, the proposed models provide valuable indications for treatment strategies and future research.

Prompt intervention is necessary since the onset of prodromal symptoms in individuals at high risk for developing BD, as indicated, for instance, by presence of family history [40]. At this stage, psychoeducation strategies should focus on avoidance of environmental stressors such as substance misuse [54] and early recognition of first-episode symptoms. Long-term treatment from the first episode, alongside with psychosocial and psychoeducational approaches addressing compliance to medication and prevention of secondary sequelae [16], including education on the disorder, healthy life style habits and physical exercise [146] may help to arrest the cycle of AL and neuroprogression, which complicates the illness course by contributing to cognitive impairment and comorbid pathologies (Table 1).

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Table 1
Actions with potentially positive effects for the prevention of cognitive impairment and allostatic load in Bipolar Disorder (“Change Compass”).

Cognitive Remediation
Healthy diet
Antioxydants
N-acetyl-L-cysteine (NAC)
Good sleep
Exercise
Comorbidities rigorously treated
Omega-3
Mood Stabilizers
Psychoeducation
Avoid overprescription
Subthreshold symptoms rigorously treated
Substance misuse avoidment

Mood-stabilizing agents increase neuroprotective factors that may help to arrest the cycle of affective episode recurrence and neural and bodily deterioration [53]. All stages of disorder require adequate mood stabilization, if necessary with more than one mood stabilizer or with adjunction of an atypical antipsychotic in order to prevent recurrences. Diminishing AL and its dramatic correlates, that influence cognitive and functional impairment and correlate to psychiatric and medical comorbidities and related mortality should be considered a gold standard for the treatment of BD.

7. Future directions

Cognitive enhancement strategies in BD are still underdeveloped and clearly insufficient. Use of medications aiming to reduce oxidative stress, modulators of glutamatergic and dopaminergic neurotransmission, neurotrophic factors and neuropeptides should be evaluated as potential treatment opportunities. Psychosocial interventions potentially including neuroregenerative interventions such as cognitive remediation, physical exercise, coping abilities and other targets should also be developed in order to revert the cycle of AL and its dramatic correlates.

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2.1.6. Predictors of recurrence to a specific episode: focus on Predominant Polarity

Emerging evidence suggests that the polarity of episodes over the course of bipolar disorder, as well as the polarity of initial or index episode may be among the strongest predictors of recurrence to a specific episode (Vieta et al.,2009; Calabrese et al., 2004). Ever since late '70s an attempt was made to classify bipolar patients according to predominance of episode polarity, when patients were divided into "predominantly manic", "predominantly depressed" and "nuclear" types (Angst, 1978). "Manic-prone" vs. "depressive-prone" patients were first analyzed in a clinical trial by Quitkin et al. (1986), and later in a community sample (Osher et al., 2000), while the first large sample was studied in STEP-BD project (Perlis et al., 1995).

The concept of "predominant polarity" was operationalized and validated by Colom et al. (2006).

A large body of evidence suggests that the predominance of polarity in bipolar disorder, defined as *at least twice as many episodes of one pole of the disorder over the other*, is a valid prognostic parameter with important clinical and therapeutic implications (Colom et al., 2006; Rosa et al., 2008; Vieta et al.,

2009). According to Colom et al., 2006, about one half of bipolar patients qualify for a specific predominant polarity. In European and American populations 50–60% of patients present predominant depressive polarity and about 40% have predominantly manic polarity (Tohen et al., 2009). Only in Israel, Osher et al. (2000) reported a predominately manic course of illness as more common and did not find any gender-related differences in type of illness course.

Predominantly manic and predominantly depressive bipolar patients present important clinical differences. Predominantly manic patients were reported to have more frequent presence of substance misuse, psychotic symptoms, higher hospitalization rate and more cognitive impairment (Colom et al., 2006; Martinez-Aran et al., 2007), while patients with predominantly depressive polarity present a higher number of suicide attempts, seasonal pattern and melancholic features (Goikolea et al., 2007; Rosa et al., 2008). Perugi et al. (2000) reported that the polarity of episodes over time reflects polarity at onset. Patients with depressive onset were reported to have higher levels of rapid cycling and a higher rate of suicide attempts, but were significantly less likely to develop psychotic symptoms (Perugi et

al., 2000).

Dell'Osso et al. (2002) reported that insight into specific aspects of the illness was related to the polarity of mood episode: patients with mania showed significantly poorer insight compared with those with mixed mania, bipolar depression and unipolar depression, which they hypothesized was due to the persistence of subsyndromal symptoms in patients remitting from a manic episode (Dell'Osso et al., 2002).

Considering these clinical differences and high prevalence of predominant polarity among bipolar patients, it is a factor that should be taken into account when implementing maintenance therapy of Bipolar Disorder.

2.2. Summary of the publications

This dissertation is based on the result of different works carried out during the Neuroscience and Endocrinometabolic Sciences Doctorate of University of Pisa, in collaboration with the Clinical Institute of Psychiatry and Psychology in Hospital Clinic of Barcelona. The following articles have been published in international journals, as a result of the work performed, with a global impact factor (IF) of 59.928.

1. Popovic, D., Reinares, M., Goikolea, J.M., Bonnin, C.M., Gonzalez-Pinto, A., Vieta, E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder (2012) European Neuropsychopharmacology, 22 (5), pp. 339-346. (IF 4.201)

2. Vieta, E., Popovic, D., Rosa, A.R., Solé, B., Grande, I., Frey, B.N., Martinez-Aran, A., Sanchez-Moreno, J., Balanzá-Martínez, V., Tabarés-Seisdedos, R., Kapczinski, F. The clinical implications of cognitive impairment and allostatic load in bipolar disorder (2012) European Psychiatry, Article in Press. (IF 2.766)

3. Popovic, D., Reinares, M., Amann, B., Salamero, M., Vieta, E. Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder (2011) Psychopharmacology, 213 (4), pp. 657-667. (IF 4.077)

4. Solé, B., Bonnin, C.M., Torrent, C., Balanzá-Martínez, V., Tabarés-Seisdedos, R., Popovic, D., Martínez-Arán, A., Vieta, E. Neurocognitive impairment and psychosocial functioning in bipolar II disorder (2012) Acta Psychiatrica Scandinavica, 125 (4), pp. 309-317. (IF 4.22)

5. Sole, B., Bonnin, C.M., Torrent, C., Martinez-Aran, A., Popovic, D., Tabarés-Seisdedos, R., Vieta, E. Neurocognitive Impairment Across the Bipolar Spectrum (2012) CNS Neuroscience and Therapeutics, 18 (3), pp. 194-200. (IF 4.443)

6. Valentí, M., Pacchiarotti, I., Bonnín, C.M., Rosa, A.R., Popovic, D., Nivoli, A.M.A., Goikolea, J.M., Murru, A., Undurraga, J., Colom, F., Vieta, E. Risk factors for antidepressant-related switch to mania (2012) Journal of Clinical Psychiatry, 73 (2), pp. e271-e276. (IF 5.8)

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2.2.1. Summary of the results

I) Popovic, D., Reinares, M., Amann, B., Salamero, M., Vieta, E. Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder (2011) Psychopharmacology, 213 (4), pp. 657-667

Rationale: Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments.

Objective: The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of bipolar disorder by means of the number needed to treat (NNT)

Methods: The efficacy of drugs used for maintenance treatment of BD, as emerging from the results of randomized controlled trials, was assessed using the size effect measure of NNT. PubMed searches were conducted on English-language articles published until May 2010 using the search terms “bipolar disorder,” “mania,” “mixed episode,” or “bipolar depression,” cross-referenced with trial characteristic search phrases and

generic names of medications. The search was supplemented by manually reviewing reference lists from identified publications.

Results: In 15 studies, aripiprazole, olanzapine, quetiapine, risperidone long-acting injection, lithium, lamotrigine, and divalproex proved effectiveness in terms of NNTs (≥10% advantage over placebo) for prevention of relapse into any mood episode. Quetiapine, lithium, risperidone long-acting injection, aripiprazole, and olanzapine are effective in manic recurrence prevention. Lamotrigine, quetiapine, and lithium present significant NNTs for prevention of depressive relapses.

Conclusions: All of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for prevention of manic and/or depressive relapses. The comparison of NNT values of the available agents may represent a useful tool in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with BD.

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REVIEW

Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder

Dina Popovic · Maria Reinares · Benedikt Amann · Manel Salamero · Eduard Vieta

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Abstract
Rationale Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments.
Objective The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of BD by means of the number needed to treat (NNT).
Methods The efficacy of drugs used for maintenance treatment of BD, as emerging from the results of randomized controlled trials, was assessed using the size effect measure of NNT. PubMed searches were conducted on English-language articles published until May 2010 using the search terms "bipolar disorder," "mania," "mixed episode," or "bipolar depression," cross-referenced with trial characteristic search phrases and generic names of medications. The search was supplemented by manually reviewing reference lists from identified publications.
Results In 15 studies, aripiprazole, olanzapine, quetiapine, risperidone long-acting injection, lithium, lamotrigine, and divalproex proved effectiveness in terms of NNTs (≥10% advantage over placebo) for prevention of relapse into any mood episode. Quetiapine, lithium, risperidone long-acting injection, aripiprazole, and olanzapine are effective in manic recurrence prevention. Lamotrigine, quetiapine, and lithium present significant NNTs for prevention of depressive relapses.
Conclusions All of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for prevention of manic and/or depressive relapses. The comparison of NNT values of the available agents may represent a useful tool in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with BD.

Keywords Bipolar disorder · NNT · Treatment efficacy · Maintenance treatment

D. Popovic · M. Reinares · M. Salamero · E. Vieta (✉)
Bipolar Disorders Program, Hospital Clinic,
University of Barcelona, IDIBAPS, CIBERSAM,
Barcelona, Catalonia, Spain
e-mail: evieta@clinic.ub.es

D. Popovic
Department of Psychiatry, Neurobiology,
Pharmacology and Biotechnology, University of Pisa,
Pisa, Italy

B. Amann
Department of Psychiatry, Hospital Benito Menni,
Sant Boi del Llobregat, CIBERSAM,
Barcelona, Spain

Introduction

The ongoing research on bipolar disorder (BD) has highlighted its pervasive and debilitating nature, characterized by lifelong recurrent episodes and residual intra-episodic symptomatology (Keck et al. 2007). Recurrence rates can reach up to 49% within 2 years of recovery from an initial episode (Perlis et al. 2006), with the polarity of the index episode which tends to predict the polarity of relapse and the risk of recurrence that increments with the number of mood episodes (Calabrese et al. 2004).

Management of BD after acute treatment of mood episodes entails first continuation therapy aiming to prevent relapses, followed by maintenance therapy focusing on prevention of recurrences (Calabrese et al. 2006). The maintenance treatment of BD continues to represent a major clinical issue. The current first-line treatment strategies for long-term treatment of bipolar disorder are represented by lithium, lamotrigine, valproate, olanzapine, quetiapine in monotherapy and as adjunctive therapy, aripiprazole for the prevention of manic events, risperidone long-acting injection monotherapy and as adjunctive therapy, and adjunctive ziprasidone for the prevention of mood events (Yatham et al. 2009).

Monotherapy trials against placebo remain the gold standard design for determining efficacy in BD (Goodwin et al. 2008). A recommended tool for reporting results of clinical trials for bipolar disorder is represented by the number needed to treat (NNT) analysis (Martinez-Aran et al. 2008). NNT summarizes the effect of treatment in terms of the number of patients a clinician needs to treat with a particular therapy to expect to prevent one adverse event. NNT is a measure of effect size, and calculation of the NNT can quantify the clinical relevance of a statistically significant study result (Citrome 2008). Although NNT has been described as "the least misleading and most clinically useful measure of treatment effectiveness" (Gray 2004), it is considered likely to help translate efficacy-driven clinical data to information that will more readily guide clinicians on the benefits of specific interventions in BD (Martinez-Aran et al. 2008). As a matter of fact, most up-to-date clinical trials in bipolar disorder have not included NNT analyses.

The aim of the present study was to evaluate and compare the effects of the pharmacological treatments used for the long-term management of bipolar disorder by the means of NNT.

Methods

We systematically reviewed randomized controlled trials (RCTs) of medications used for the treatment of any phase of BD. A comprehensive PubMed search of all English-language articles published up to April 2010 was performed. Terms "bipolar disorder," "mania," "mixed episode," or "bipolar depression" were cross-referenced with trial characteristics search phrases and generic names of medications used for maintenance treatment of BD. The search was supplemented by manually reviewing reference lists from the identified publications.

Included RCTs assessed the effectiveness of drugs in the treatment of BD compared to placebo with a minimal duration of 6 months and in patients aged over 18. Exclusion criteria were a small sample size (meaning median sample inferior to 16.5 subjects in each group as suggested by Richy et al. 2004), a study sample not exclusively composed of bipolar patients, the use of rating scales not validated in patients with bipolar disorder, and an absence of a placebo control group.

NNT for prevention of relapse into any episode, mania, and depression for the drugs used for long-term management of BD compared to placebo were calculated from the reports of all the studies that fulfilled the inclusion criteria.

Statistical methods

NNT can be expressed as the reciprocal of the absolute risk reduction, and is calculated by taking the reciprocals of the differences between the rates of the outcomes for two interventions, and rounding upwards to the next whole number. Only NNTs <10 are considered clinically meaningful. Lower NNTs reflect larger clinical difference between the comparisons. NNTs of 3, 4 and 9, corresponding to values of Cohen's d of 0.8, 0.5 and 0.2, represent "large," "medium," and "small" effect sizes (Kraemer and Kupfer 2006; Cook and Sackett 1995).

In addition, a 95% confidence interval (CI) for the NNT was calculated, constructed by inverting and exchanging the limits of a 95% CI for the absolute risk reduction (Cook and Sackett 1995). When the treatment effect is significant at the 5% level, the 95% CI for the absolute risk reduction will not include zero, and thus the 95% CI for the NNT will not include infinity (Altman 1998).

Two competing methods have been proposed in order to calculate NNT from results of systematic reviews; one method involves calculating the NNT from meta-analytical estimates, the other by treating the data as if it all arose from a single trial. Altman and Deeks (2002) found the "treat-as-one-trial" method to be susceptible to bias when there were imbalances between groups within one or more trials in the meta-analysis (Simpson's paradox). In this paper, we have followed their suggestion not to use the treat-as-one-trial method of calculating NNTs, thus, when more RCTs regarding a single agent were available, we reported NNTs for data reported in each trial separately.

We have proceeded to calculate NNTs for the prevention of any kind of recurrences, followed by NNTs of manic and depressive episodes for each treatment assessed, as reported in the original studies.

Results

Included studies

Fifteen out of 67 available studies have met the inclusion criteria. Patient characteristics and primary outcomes of the selected studies have been reported in the original

publications. All studies included an acute treatment phase, followed by a double-blind, relapse-prevention (maintenance) treatment phase. Some of the RCTs used a three-arm design thus could be used to make two comparisons each. In some cases, two or more articles/references provide data for the same RCT.

Table 1 illustrates the available studies comparing therapeutic agents for maintenance therapy of bipolar mood episodes commonly prescribed for the long-term treatment of bipolar disorder with placebo.

Table 2 shows rates of relapse into any mood episode, mania, and depression as published in the original articles.

Table 3 provides the NNT versus placebo for recurrence prevention for any mood episode and for manic and depressive episodes specifically for several treatments of interest.

Pharmacological agents used in maintenance treatment of bipolar disorder

Aripiprazole

The only relapse-prevention study conducted on aripiprazole in BD I patients showed that aripiprazole 15–30 mg/day was significantly superior to placebo in prevention of relapse into any mood episode during a 100-week-long double-blind treatment, with an NNT value of 6 (Keck et al. 2007).Aripiprazole was significantly superior to placebo in preventing relapse to mania, which translates into an NNT of 7. No difference in prevention of depressive relapses was noted between aripiprazole and placebo.

Given that efficacy was shown for the prevention of any mood episode and for mania in particular, aripiprazole represents a first-line option for treatment and prevention of mania in maintenance treatment of bipolar disorder.

Olanzapine

Two placebo-controlled studies with maintenance treatment phases of 12 and 18 months were available for NNT analyses (Tohen et al. 2006, 2004).

When comparing olanzapine to placebo over 12 months (Tohen et al. 2006), the NNT was three for prevention of symptomatic relapse to any mood episode, indicating a large clinical maintenance effect size difference between olanzapine and placebo. When olanzapine plus lithium or valproate was compared with placebo plus lithium or valproate over an 18-month period, the NNT for the prevention of any episode was not significant.

Furthermore, olanzapine showed a significant difference in the risk of relapse into manic episodes over placebo for up to 12 months (Tohen et al. 2006), corresponding to an NNT of 5; however, no significant differences emerged from the study comparing olanzapine combined with lithium or valproate with placebo combined with lithium or valproate over 18 months (Tohen et al. 2004). Olanzapine in monotherapy or combined with lithium or divalproex was not significantly superior to placebo in preventing relapse into depressive episodes (Tohen et al. 2006).

Overall, olanzapine in monotherapy has proven efficacy for prevention of any mood episode as well as manic episodes. Although olanzapine combined with lithium or valproate (Tohen et al. 2004) had an NNT of six for prevention of any mood episode, as well as of depression, it cannot be considered significant since CI crossed infinity.

Quetiapine

Three placebo-controlled randomized double-blind studies assessed the efficacy of quetiapine in long-term treatment of BD I (Vieta et al. 2008a, b; Suppes et al. 2009; Weisler et al. 2008).

Two studies (Vieta et al. 2008a; Suppes et al. 2009) assessing effectiveness of quetiapine as add-on therapy during continuation treatment for up to 104 weeks demonstrated that quetiapine in combination with lithium or divalproex was significantly more effective than lithium or divalproex alone in the prevention of mood episodes, which translates into an NNT of 4. In a recent study by Weisler et al. (2008), evaluating quetiapine as monotherapy for up to 104 weeks, quetiapine was found effective in the prevention of any mood episode, with an NNT of 3.

Quetiapine in combination with lithium or divalproex was significantly more effective than the placebo in combination with lithium or divalproex in preventing recurrence of mania, assuming an NNT value of seven in the study by Vieta et al. (2008a) and nine in the study by Suppes et al. (2009). Likewise, quetiapine in monotherapy (Weisler et al. 2008) was significantly more effective than placebo in the prevention of mania, with an NNT of 3.

NNTs were significant for quetiapine plus lithium or divalproex in preventing depressive relapses in the two studies evaluating quetiapine as adjunctive therapy, with values of 7 (Vieta et al. 2008a) and 6 (Suppes et al. 2009). Quetiapine in monotherapy assumed an NNT value of 4 in the prevention of depressive episodes (Weisler et al. 2008).

Taken together, these data indicate that quetiapine alone and combined with lithium or valproate was effective in preventing any mood episode and has a similar efficacy for prevention of mania and depression.

Risperidone long-acting injection

Although the long-term efficacy of oral risperidone has not yet been assessed (Yatham et al. 2009), two RCTs have examined the efficacy of risperidone long-acting injection

Table 1 Characteristics of included randomized controlled studies

Trial (in order of appearance in text)	Patient inclusion criteria (maintenance phase)	Duration (weeks)	Number randomized	Dosage (mg/day) or plasma levels/mean dosage
Keck et al. (2007)	Bipolar I≥18 years YMRS≤10 MADRS≤13	100	ARI=78 PLA=83	ARI, 15–30 mg/day; mean, 23.8 mg/day
	No hospitalization in previous 3 months			
Tohen et al. (2006)	Bipolar I ≥18 years YMRS≤12	48	OLZ=225 PLA=136	OLZ, 5–20 mg/day
	HAM-D≤8			
	Two prior mixed or manic episodes in the past 6 years			
Tohen et al. (2004)	Bipolar I	72	LI/VPA+PLA=48	OLZ, 5–20 mg/day; mean, 12.5 mg/day
	18–70 years		LI/VPA+OLZ=51	LI, 0.66–0.86 mEq/L
	YMRS≤12 HRSD-21≤8			VPA, 60.1–73.8 μg/mL
Vieta et al. (2008a)	Bipolar I	104	QUE+LI/VPA=336	QUE, 400–800 mg/day; mean, 497 mg/day
	≥18 years		PLA+LI/VPA=367	LI, 0.5–1.2 mEq/L
	YMRS≤12 HAM-D≤12			VPA, 50–125 μg/mL
Suppes et al. (2009)	Bipolar I	104	QUE+LI/VPA=310	QUE, 400–800 mg/day; mean, 519 mg/day
	≥18 years YMRS≤10		PLA+LI/VPA=313	LI, 0.5–1.2 mEq/L
	MADRS≤13			Mean, 0.71–0.74 mEq/L
				VPA, 50-125 μg/mL
				Mean, 68.91–71.38 μg/mL
Weisler et al. (2008)	Bipolar I	104	QUE=404	QUE, 300–800 mg/day
	≥18 years YMRS≤12 MADRS≤12 Acute current or recent (past 26 weeks) manic, depressive, or mixed index episode treated with QUE		LI=364 PLA=404	Li, 0.6–1.2 mEq/L
Quiroz et al. (2010)	Bipolar I 18–65 years Recent manic/mixed episode or stable patients with≥1 mood episode in past 4 months	96	RLAI=140 PLA=136	RIS, 12.5–50 mg i.m.; mean, 25 mg
Macfadden et al. (2009)	Bipolar I 18–70 years ≥4 episodes in the past year	52	RLAI+TAU=65 PLA+TAU=59	RLAT, 25–50 mg/2 weeks
Bowden et al. (2010)	Bipolar I	24	ZIP+LI/VPA=127	ZIP, 80–160 mg/day
	≥18 years		PLA+LI/VPA=113	LI, 0.6–1.2 mEq/L
	Current or recent manic/mixed episode			Mean, 0.7–0.9 mEq/L
				VPA, 50–125 μg/mL; mean, 67.4–72.8
Bowden et al. (2003)	Bipolar I	76	LAM=59	LAM, 100–400 mg/day
	≥18 years Current or recent (hypo)mania≥1 additional (hypo)manic and 1 depressive episode in the past 3 years		LI=46 PLA=70	LI, 0.8–1.1 mEq/L
Calabrese et al. (2003)	Bipolar I	72	LAM=221	LAM, 50–400 mg/day; mean, 200 mg/day
	≥18 years Current or recent MDE ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years		LI=121 PLA=121	LI, 0.8–1.1 mEq/L; mean, 0.8±0.3 mEq/L

Table 1 (continued)

Trial (in order of appearance in text)	Patient inclusion criteria (maintenance phase)	Duration (weeks)	Number randomized	Dosage (mg/day) or plasma levels/mean dosage
Calabrese et al. (2000)	Bipolar I and II, rapid cycling ≥18 years ≤14 HAM-D ≤12 MRS <3 on item 3 HAM-D stable for 4 weeks	26	LAM=90 PLA=87	LAM, 100–300 mg/day
Prien et al. (1973)	Manic–depressive, manic type	24[a]	LI=101 PLA=104	LI, 0.5–1.4 mEq/L
Bowden et al. (2000)	Bipolar I 18–70 years Manic episode≤3 months before randomization MRS≤11 DSS≤13 GAS>60, no serious suicidal risk	52	VPA=187 LI=90 PLA=92	VPA, 71–125 μg/mL LI, 0.8–1.2 mmol/L
Vieta et al. (2008b)	Bipolar I or II ≥18 years YMRS≤12 MADRS≤20 No acute phases in 6 months	52	OXC+LI=26 PLA+LI=29	OXC, 1,200 mg/day LI, 0.6 mEq/L

PLA placebo, *ARI* aripiprazole, *OLZ* olanzapine, *LI* lithium, *VPA* valproate, *QUE* quetiapine, *TAU* treatment as usual, *ZIP* ziprasidone, *LAM* lamotrigine, *OXC* oxcarbazepine

[a] *NNT* analyses refer to 12-month period

(RLAI) for maintenance treatment in BD (Quiroz et al. 2010; Macfadden et al. 2009).

A recent study examined the long-term efficacy of RLAI (Quiroz et al. 2010) in patients with recent manic or mixed episode followed up for up to 24 months.

RLAI monotherapy was shown to be superior to placebo in preventing any mood episode with an NNT of 4. A study conducted by Macfadden et al. (2009) assessed RLAI as an adjunct to treatment as usual for 52 weeks in 139 patients who had frequently relapsing BD. Significantly fewer patients in the adjunctive RLAI group relapsed into any mood episode compared with those in the placebo group, corresponding to an NNT of 5.

When comparing RLAI to placebo over 24 months (Quiroz et al. 2010), NNT was four for the prevention of manic recurrences and eight in the 52-week follow-up trial conducted by Macfadden et al. (2009).

NNT was not significant for the prevention of depressive episodes in either available study (Quiroz et al. 2010; Macfadden et al. 2009).

Overall, RLAI has proven efficacy for the prevention of any kind of mood episodes, as well as for the prevention of mania while it did not result effective for the prevention of depressive episodes.

Ziprasidone

The efficacy of adjunctive ziprasidone for maintenance treatment of bipolar mania was demonstrated in a recent 6-month-long RCT in 239 patients with BD I (Bowden et al. 2010). When comparing ziprasidone to placebo, NNT assumed the value of 8 for the prevention of any mood episode while it was not significant for the prevention of manic or depressive episodes (Fig. 1).

Lamotrigine

Two RCTs compared lamotrigine, lithium, and placebo in maintenance treatment of recently manic (Bowden et al. 2003) and depressed (Calabrese et al. 2003) bipolar I patients. Since the studies were prospectively designed for combined analyses, a pooled analysis from the two abovementioned studies (Goodwin et al. 2004), allowing greater power with respect to the original studies, was available for NNT analysis and therefore included in the present paper. An additional double-blind, placebo-controlled study examining lamotrigine as maintenance monotherapy for rapid-cycling bipolar patients was available for NNT analysis exclusively for prevention of any mood episode (Calabrese et al. 2000).

Table 2 Relapse rates reported in randomized controlled trials of pharmacological agents used for maintenance treatment of bipolar disorder

	Any episode *n* (%)		Mania *n* (%)		Depression *n* (%)	
	PCB relapse	Drug relapse	PCB relapse	Drug relapse	Placebo relapse	Drug relapse
Aripiprazole	43/83	25/77	23/83	9/77	13/83	11/77
(Keck et al. 2007)	51.81	32.47	27.71	11.69	15.66	14.28
Olanzapine	109/136	105/225	44/136	27/225	53/136	68/225
(Tohen et al. 2006)	80.14	46.66	32.35	12	38.97	30.22
Olanzapine combined with	21/38	11/30	11/38	6/30	15/38	7/30
lithium/divalproex (Tohen et al. 2004)[a]	55.26	36.66	28.94	20	39.47	23.33
Quetiapine combined with	180/367	62/336	96/367	36/336	84/367	26/336
lithium/divalproex (Vieta et al. 2008a, b)	49.04	18.53	26.16	10.71	22.89	7.74
Quetiapine combined with	163/313	63/310	61/313	22/310	102/313	41/310
lithium/divalproex (Suppes et al. 2009)	52.08	20.32	19.49	19.49	32.59	13.23
Quetiapine	343/404	162/404	291/404	121/404	186/404	65/404
(Weisler et al. 2008)	84.90	40.10	72.03	29.95	46.04	16.09
Risperidone LAI	76/135	42/140	62/135	22/140	41/135	14/135
(Quiroz et al. 2010)	56.29	30	45.93	15.71	10.37	14.29
Risperidone LAI+	27/59	15/65	12/59	5/65	11/59	8/65
treatment as usual (Macfadden et al. 2009)	45.76	23.08	20.34	7.69	18.64	12.31
Ziprasidone combined with	36/111	25/127	14/111	7/127	16/111	16/127
lithium/divalproex (Bowden et al. 2010)	32.43	19.69	12.61	5.51	14.41	12.60
Lamotrigine	49/70	28/59	22/70	16/59	21/70	8/59
(Bowden et al. 2003)	70	47.46	31.43	27.12	30	13.56
Lamotrigine	66/119	115/215	19/119	38/215	47/119	77/215
(Calabrese et al. 2003)	55.46	53.49	15.97	17.67	39.50	35.81
Lamotrigine	64/87	53/90	N.A.	N.A.	N.A.	N.A.
(Calabrese et al. 2000)	73.56	58.89				
Lamotrigine	115/191	143/280	47/191	58/280	68/191	85/280
(Goodwin et al. 2004)	60.21	51.07	24.61	20.71	35.60	30.36
Lithium	71/104	36/101	53/104	23/101	14/104	9/101
(Prien et al. 1973)	68.27	35.64	50.96	22.77	13.46	8.91
Lithium	115/191	74/167	47/191	18/167	68/191	56/167
(Goodwin et al. 2004)	60.21	44.31	24.61	10.78	35.60	33.53
Lithium	49/70	18/46	22/70	6/46	21/70	10/46
(Bowden et al. 2003)	70	39.13	31.43	13.04	30	21.74
Lithium	66/119	56/120	19/119	10/120	47/119	46/120
(Calabrese et al. 2003)	55.16	46.67	15.97	8.93	33.50	38.33
Lithium	36/94	28/91	21/94	19/91	15/94	9/91
(Bowden et al. 2000)	38.30	30.77	22.34	20.80	9.89	15.96
Lithium	343/404	149/364	291/404	102/364	186/404	66/364
(Weisler et al. 2008)	84.90	40.93	72.03	28.02	46.04	18.13
Valproate	36/94	45/187	21/94	33/187	15/94	12/187
(Bowden et al. 2000)	38.29	24.06	22.34	17.65	15.96	6.42
Oxcarbazepine combined with lithium	17/29	10/26	8/29	4/26	9/29	3/26
(Vieta et al. 2008a, b)	58.62	38.46	27.58	15.38	31.03	11.54

[a] Data referring to symptomatic relapse

Table 3 NNT values for recurrence prevention of pharmacological agents used for maintenance treatment of bipolar disorder compared to placebo

	NNT any episode (95% CI)	NNT mania (95% CI)	NNT depression (95% CI)
Aripiprazole (Keck et al. 2007)	**6** (2.9–23)	**7** (3.6, 24.9)	50.0 (7.7, infinity)
Olanzapine (Tohen et al. 2006)	**3** (2.3, 4.2)	**5** (3.4, 8.8)	12 (5.3, infinity)
Olanzapine combined with Lithium/Divalproex (Tohen et al. 2004)[a]	6 (2.4, infinity)	12 (3.4, infinity)	6 (2.6, infinity)
Quetiapine combined with Lithium/Divalproex (Vieta et al. 2008a, b)	**4** (2.7–4.2)	**7** (4.8, 10.1)	**7** (4.9, 10.0)
Quetiapine combined with Lithium/Divalproex (Suppes et al. 2009)	**4** (2.6, 4.1)	**9** (5.7, 14.0)	**6** (3.9, 7.7)
Quetiapine (Weisler et al. 2008)	**3** (2, 2.6)	**3** (2, 2.8)	**4** (2.8, 4.2)
Risperidone LAI (Quiroz et al. 2010)	**4** (2.4, 5.6)	**4** (2.5, 5.0)	26 (8.6, infinity)
Risperidone LAI+Treatment as Usual (Macfadden et al. 2009)	**5** (2.6, 15.7)	**8** (4.0, 198.7)	16 (5.2, infinity)
Ziprasidone combined with Lithium/Divalproex (Bowden et al. 2010)	**8** (4.2, 61.5)	15 (6.9, infinity)	56 (9.5, infinity)
Lamotrigine (Bowden et al. 2003)	**5** (2.6, 17.0)	24 (5.0, infinity)	7 (3.3, 38.5)
Lamotrigine (Calabrese et al. 2003)	51 (7.6, infinity)	59 (10.0, infinity)	28 (6.9, infinity)
Lamotrigine (Calabrese et al. 2003)	**7** (3.5, 108.8)	N.A.	N.A.
Lamotrigine (Goodwin et al. 2004)	11 (5.5, 1764.7)	26 (8.6, infinity)	20 (7.2, infinity)
Lithium (Prien et al. 1973)	**4** (2.2, 5.1)	**4** (2.5, 6.4)	22 (7.6, infinity)
Lithium (Goodwin et al. 2004)	**7** (3.8, 17.7)	**8** (4.6, 16.3)	49 (8.4, infinity)
Lithium (Bowden et al. 2003)	**4** (2.3, 20.5)	**6** (3, 26.4)	13 (4.1, infinity)
Lithium (Calabrese et al. 2003)	12 (4.7, infinity)	14 (6.3, infinity)	86 (7.4, infinity)
Lithium (Bowden et al. 2000)	14 (4.7, infinity)	69 (7.5, infinity)	17 (6.4, infinity)
Lithium (Weisler et al. 2008)	**3** (2, 2.6)	**3** (2.2, 2.7)	**4** (2.8, 4.4)
Valproate (Bowden et al. 2000)	**7** (3.9, 37.7)	22 (6.8, infinity)	11 (5.6, 74.3)
Oxcarbazepine combined with Lithium (Vieta et al. 2008a, b)	5 (2.2, infinity)	9 (3.0, infinity)	6 (2.5, infinity)

Significant NNTs are in bold numbers

[a] Data referring to symptomatic relapse

N.A.= Not available

When compared to placebo, lamotrigine in monotherapy was found to be effective in the prevention of any mood episode in recently manic patients (Bowden et al. 2003) with an NNT of 5, and showed no significant difference in recently depressed patients (Calabrese et al. 2003). Data emerging from the pooled analyses (Goodwin et al. 2004) evidenced an NNT of 11 for prevention of any mood episode.

Lamotrigine was not significantly superior to placebo in the prevention of mania in any of the abovementioned studies (Bowden et al. 2003; Calabrese et al. 2003; Goodwin et al. 2004).

Lamotrigine was found to be superior to placebo in preventing depressive episodes in recently manic patients (Bowden et al. 2003), with an NNT value of 7. In contrast, lamotrigine was not significantly superior to placebo in the prevention of depressive episode neither in recently depressed patients (Calabrese et al. 2003) nor in the pooled analyses (Goodwin et al. 2004).

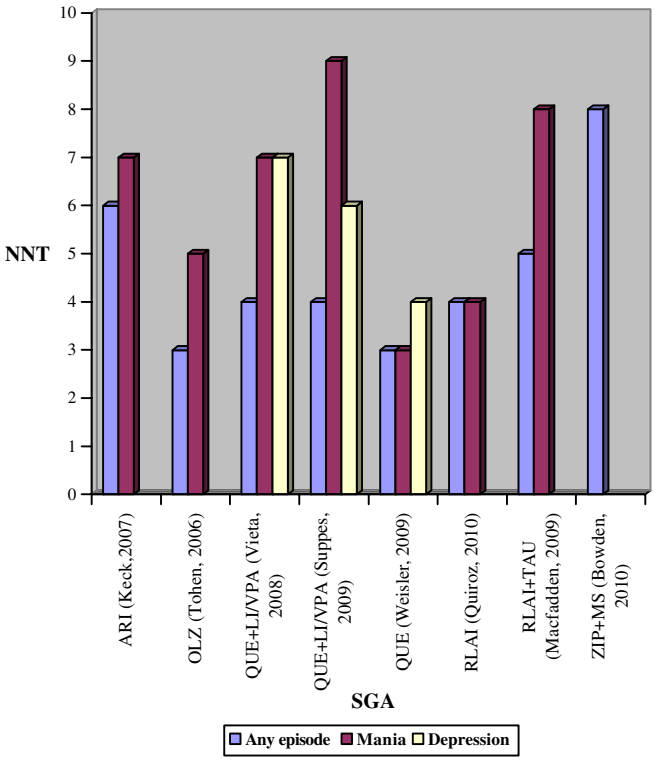
Lamotrigine in monotherapy was found effective in preventing any kind of mood episode. Its effectiveness was also demonstrated for the prevention of depressive episodes in recently manic patients.

Lithium

Although lithium has been considered to be the cornerstone of bipolar disorder maintenance treatment for many years, since the mid 1970s until 2000, no RCTs assessing lithium efficacy were published (Coryell 2009).

Only one of the studies on lithium conducted in the 1970s satisfied the inclusion criteria. A double-blind trial by Prien et al. (1973) assessed the efficacy of lithium over a 2-year period. NNT analyses relevant to a 1-year period evidenced effectiveness of lithium in preventing any mood episode, translating to an NNT of 4.

Four recent double-blind studies examined the efficacy of lithium as a maintenance treatment (Bowden et al. 2000,



SGA= second generation antipsychotic, MS= mood stabilizer, PLA=placebo, ARI= aripiprazole, OLZ= olanzapine, LI=lithium, VPA= valproate, QUE=quetiapine, RLAI= risperidone long acting injection, TAU= treatment as usual, ZIP=ziprasidone

Fig. 1 Second-generation antipsychotics in maintenance treatment of bipolar disorder (significant NNTs) *SGA* second-generation antipsychotic, *MS* mood stabilizer, *PLA* placebo, *ARI* aripiprazole, *OLZ* olanzapine, *LI* lithium, *VPA* valproate, *QUE* quetiapine, *TAU* treatment as usual, *ZIP* ziprasidone

2003; Calabrese et al. 2003; Weisler et al. 2008). In the study by Bowden et al. (2000), lithium was not significantly superior to placebo in preventing mood episodes over 1 year in a cohort of 372 patients with BD I. In two studies (Bowden et al. 2003; Calabrese et al. 2003), both previously described, lithium was studied as an active comparator medication compared to a lamotrigine-enriched sample of patients with BD I. In the study by Bowden et al. (2003), lithium was found to be significantly more effective than placebo in preventing any mood episode, with an NNT of 4 while in recently depressed BD I patients the difference was not significant. In a pooled analysis of the two studies (Goodwin et al. 2004), lithium was significantly more effective than placebo in preventing any mood episode, with an NNT value of 7. In a recent RCT conducted by Weisler et al. (2009) where bipolar I patients were followed up for up to 104 weeks, lithium, assessed as active comparator, has proven its effectiveness in preventing any kind of mood episode, with an NNT of 3.

Regarding the prevention of manic episodes, in the study by Prien et al. (1973) lithium was effective in the prevention of manic episodes, with an NNT of 4. Lithium was also found to be significantly more effective than placebo in preventing mania in recently manic patients (Bowden et al. 2003), with an NNT of 2, as well as in pooled analyses of the two studies (Goodwin et al. 2004). Likewise, in the study by Weisler et al. (2009), lithium assumed an NNT value of three for mania prevention; however, lithium was not significantly superior to placebo in preventing manic recurrences in the remaining two studies (Bowden et al. 2000; Calabrese et al. 2003).

Lithium was found significantly superior to placebo in preventing depressive episodes, with an NNT of 4, only in the study by Weisler et al. (2009) while it resulted not significantly superior to placebo in preventing depression in any other of the abovementioned studies (Prien et al. 1973; Bowden et al. 2000; Bowden et al. 2003; Calabrese et al. 2003; Goodwin et al. 2004).

In conclusion, since the efficacy of lithium was largely demonstrated for the prevention of any mood episode, in particular for mania, lithium continues to represent a first-line maintenance treatment for bipolar disorder for the treatment and prevention of mania.

Valproate

Only one study assessing valproate in maintenance treatment of bipolar disorder was available for NNT analyses. A

randomized, double-blind, parallel-group multicenter study of treatment outcomes was conducted over a 52-week maintenance period (Bowden et al. 2000). Patients with a previous manic episode were randomized to maintenance treatment with divalproex, lithium, or placebo. Although the authors concluded that the treatment arms did not differ significantly on time to recurrence of any mood episode during maintenance therapy, the NNT for prevention of any mood episode was 7; however, valproate did not result superior to placebo in preventing neither manic nor depressive episodes.

Oxcarbazepine

One RCT assessed the efficacy of oxcarbazepine compared to placebo as adjuncts to ongoing treatment with lithium in 55 patients with BD I and BD II for a period of 52 weeks (Vieta et al. 2008b). The results evidenced a lower risk of recurrence to any mood episode with oxcarbazepine, corresponding to an NNT of 5, but this difference was not significant since the CI crossed infinity. The same was true for the prevention of manic and depressive episodes, with NNT values of 9 and 6, respectively, neither statistically significant (Fig. 2).

Discussion

Due to the episodic and chronic nature of the illness, maintenance therapy is a critical part of treatment for bipolar disorder. The ultimate goal of treatment is the prevention of episode recurrence through the long-term management of the symptoms (Thase 2008).

NNT is a useful and meaningful concept for practicing clinicians which may help to translate the results of randomized controlled clinical trials to evidence-based medicine (Martinez-Aran et al. 2008). Nonetheless, most of the published studies have not reported NNT values for assessed medicaments. To the best of our knowledge this is the first paper providing NNTs for all available placebo-controlled trials for agents used in long-term treatment of BD.

NNT analysis evidenced differences in efficacy profiles among various agents used for the maintenance treatment for bipolar disorder. In general, our findings are in agreement with the recommendations of recent guidelines for the maintenance therapy of bipolar disorder (Yatham et al. 2009). Aripiprazole, olanzapine, quetiapine, risperidone LAI, ziprasidone, lithium, lamotrigine, and valproate have single-digit NNTs and are significantly effective for the

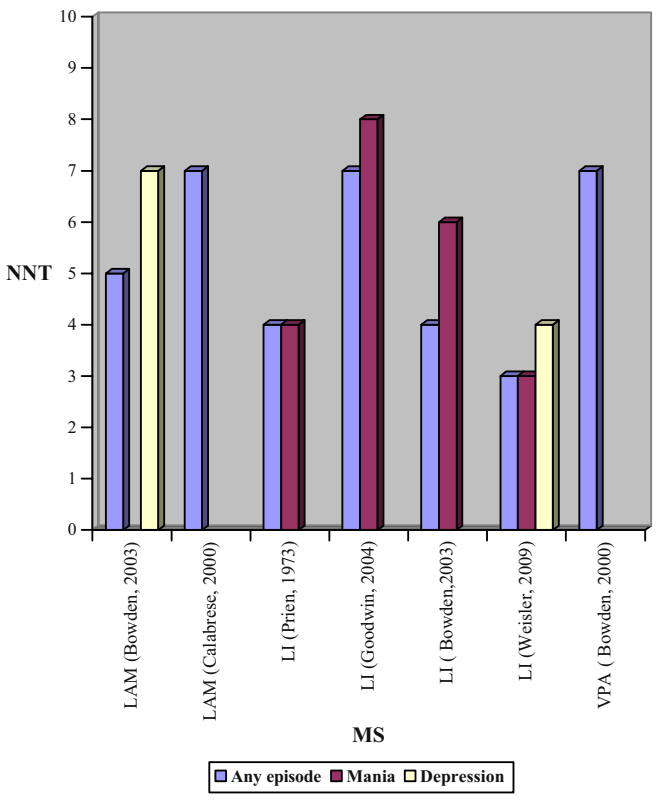


Fig. 2 Mood stabilizers in maintenance treatment of bipolar disorder (significant NNTs) *SGA* second-generation antipsychotic, *MS* mood stabilizer, *PLA* placebo, *LI* lithium, *VPA* valproate, *LAM* lamotrigine

SGA= second generation antipsychotic, MS= mood stabilizer, PLA=placebo, LI=lithium, VPA= valproate, LAM=lamotrigine

prevention of any mood episode, but show substantial differences as to their ability to prevent mania and depression separately. Among the agents assessed, the only exception is given by oxcarbazepine combined with lithium that had a significant single-digit NNT for prevention of any episode, mania, and depression, but CI did not result significant, probably for the lack of power due to the relatively small sample size.

The NNT analyses confirmed the efficacy of quetiapine (in monotherapy and combined with mood stabilizer), lithium, risperidone LAI, aripiprazole, and olanzapine in preventing manic recurrences. Lamotrigine, lithium, and quetiapine alone and combined with lithium/valproate presented significant NNTs for the prevention of depressive relapses. The data emerging from our analysis provide utter evidence that the treatments assessed differentiated in terms of whether they primarily prevent mania or depression or have bidirectional effects. The clinical relevance of the directional efficacy of the various medications is heightened in the context of predominant polarity, a parameter correlated with treatment response and outcome of later acute episodes (Vieta et al. 2009; Colom et al. 2006); nevertheless, placebo-controlled randomized clinical trials assessing long-term effectiveness of mood stabilizers and antipsychotics are surprisingly sparse, and important questions remain unanswered.

In order to present the most complete data available, we have included both RCTs assessing drugs in monotherapy as well as combined with mood stabilizers such as lithium and valproate. The studies were not completely homogeneous with respect to clinical characteristics of the sample (rapid-cycling course, manic/mixed states or depression, refractory patients or unbiased samples), sample size, and rates of study completion, which may compromise to some extent the generalizability of reported NNTs.

In the interest of brevity, we have not addressed the number needed to harm analysis, although medication selection is based on tolerability as well as effectiveness. NNTs for the prevention of mixed episodes were omitted since most available RCTs have not proceeded to such assessment and the number of events in the trials that did look at it was extremely small.

An apparent paradox emerges from NNT values analyses. Namely, it may seem surprising that NNT for the prevention of any mood episode is often smaller than NNT for the prevention of manic or depressive relapses separately; however, one should bear in mind that the included studies were designed to assess efficacy in terms of prevention of any mood episode as primary aim. NNT for prevention of any mood episode reflects the sum of effects that a drug has upon any episode, manic, depressive, mixed, or unknown type, conferring it more power than any episode taken singularly; thus a drug may perform better overall in comparison to its best effect upon a single episode.

Successful long-term management often appears to require combination treatment, and although assessing combined treatments went beyond the aims of our study, lack of such trials, e.g., lamotrigine as add-on treatment, should be an object of future research. Further studies are needed in order to address the long-term effectiveness of agents such as carbamazepine, oxcarbazepine, and valproate. Some antipsychotics, such as amisulpride, asenapine, or paliperidone have not been assessed in long-term placebo-controlled studies.

Conclusions

The present review of clinical effectiveness by the means of NNT comparison aimed to investigate all pharmacological treatments approved as maintenance therapy in BD. Most of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for the prevention of manic and/or depressive relapses. The comparison of NNT values of the available medicaments may represent a useful adjuvant in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with BD.

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II) Popovic, D., Reinares, M., Goikolea, J.M., Bonnin, C.M., Gonzalez-Pinto, A., Vieta, E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder (2012) European Neuropsychopharmacology, 22 (5), pp. 339-346.

Over one half of bipolar patients have been reported to be more prone to either depressive or manic relapses. This study aimed to define profiles of drugs used for maintenance treatment of bipolar disorder (BD) by the means of Polarity Index. Polarity Index is a new metric indicating the relative antimanic versus antidepressive preventive efficacy of drugs. Polarity Index was retrieved by calculating Number Needed to Treat (NNT) for prevention of depression and NNT for prevention of mania ratio, as emerging from the results of randomized placebo-controlled trials.

Included trials were randomized and double blind, with a minimal duration of 24 weeks, assessing effectiveness of a mood stabilizer or antipsychotic drug alone or in combination with a mood stabilizing agent versus a placebo comparator in BD maintenance treatment. Polarity Index value above 1.0 indicates a relative greater antimanic prophylactic efficacy, number below

1.0 a relative greater antidepressive efficacy. The polarity index for the drugs used in maintenance therapy for bipolar disorder was 12.09 for risperidone, 4.38 for aripiprazole, 3.91 for ziprasidone, 2.98 for olanzapine, 1.39 for lithium, 1.14 for quetiapine, and 0.40 for lamotrigine.

Polarity index of valproate and oxcarbazepine may not be reliable due to the failure of their maintenance trials. The polarity index provides a measure of how much antidepressant versus antimanic a drug is in bipolar disorder prophylaxis, and may guide the choice of maintenance therapy in bipolar patients.

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Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder

Dina Popovic [a,b], Maria Reinares [a], Jose Manuel Goikolea [a], Caterina Mar Bonnin [a], Ana Gonzalez-Pinto [c], Eduard Vieta [a,*]

[a] *Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain*
[b] *Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Italy*
[c] *Santiago Apóstol Hospital, University of the Basque Country, CIBERSAM, Vitoria, Spain*

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Bipolar disorder;
Polarity Index;
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Maintenance treatment;
Mood stabilizers;
Antipsychotics

Abstract

Over one half of bipolar patients have been reported to be more prone to either depressive or manic relapses. This study aimed to define profiles of drugs used for maintenance treatment of bipolar disorder (BD) by the means of Polarity Index. Polarity Index is a new metric indicating the relative antimanic *versus* antidepressive preventive efficacy of drugs. Polarity Index was retrieved by calculating Number Needed to Treat (NNT) for prevention of depression and NNT for prevention of mania ratio, as emerging from the results of randomized placebo-controlled trials. Included trials were randomized and double blind, with a minimal duration of 24 weeks, assessing effectiveness of a mood stabilizer or antipsychotic drug alone or in combination with a mood stabilizing agent *versus* a placebo comparator in BD maintenance treatment. Polarity Index value above 1.0 indicates a relative greater antimanic prophylactic efficacy, number below 1.0 a relative greater antidepressive efficacy. The polarity index for the drugs used in maintenance therapy for bipolar disorder was 12.09 for risperidone, 4.38 for aripiprazole, 3.91 for ziprasidone, 2.98 for olanzapine, 1.39 for lithium, 1.14 for quetiapine, and 0.40 for lamotrigine. Polarity index of valproate and oxcarbazepine may not be reliable due to the failure of their maintenance trials. The polarity index provides a measure of how much antidepressant *versus* antimanic a drug is in bipolar disorder prophylaxis, and may guide the choice of maintenance therapy in bipolar patients.

1. Introduction

Ever since late '70s an attempt was made to classify bipolar patients according to predominance of episode polarity when patients were divided into "predominantly manic", "predominantly depressed" and "nuclear" types (Angst,

* Corresponding author at: Hospital Clinic, Villarroel 170, Barcelona 08036, Catalonia, Spain. Tel.: +34 932 275 401; fax: +34 932 279 876.
E-mail address: evieta@clinic.ub.es (E. Vieta).

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Table 1 Characteristics and reported results of included randomized controlled studies.

Trial characteristics				Study results			
Drug	Trial	Patient inclusion criteria (maintenance phase)	Duration (weeks)	Manic relapse		Depressive relapse	
				PBO relapse	Drug relapse	PBO relapse	Drug relapse
Aripiprazole	Keck et al., 2007	Bipolar I YMRS ≤10 MADRS ≤13 No hospitalization in previous 3 months	100	23/83 27.71%	9/77 11.69%	13/83 15.66%	11/77 14.28%
Aripiprazole combined with lithium/divalproex	Marcus et al., 2011	Bipolar I YMRS ≥16 Curent or recent manic/mixed episode Inadequate response to lithium or valproate YMRS ≥16 and ≤35% decrease from baseline at 2 weeks	52	25/169 14.79%	8/168 4.76%	22/169 13.02%	17/168 10.12%
Lamotrigine	Bowden et al., 2003	Bipolar I Current or recent (hypo)mania ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	76	22/70 31.43%	16/59 27.12%	21/70 30.00%	8/59 13.56%
Lamotrigine	Calabrese et al., 2003	Bipolar I Current or recent MDE ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	72	19/119 15.97%	38/215 17.67%	47/119 39.50%	77/215 35.81%
Lithium	Bowden et al., 2003	Bipolar I Current or recent (hypo)mania ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	76	22/70 31.43%	6/46 13.04%	21/70 30%	10/46 21.74%
Lithium	Bowden et al., 2000	Bipolar I Manic episode ≤3 months before randomization. MRS ≤11 DSS ≤13 GAS >60, No serious suicidal risk	52	21/94 22.34%	19/91 20.88%	15/94 15.96%	9/91 9.89%
Lithium	Calabrese et al., 2003	Bipolar I Current or recent MDE ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	72	19/119 15.97%	10/120 8.33%	47/119 39.50%	46/120 38.33%
Lithium	Prien et al., 1973	Manic-depressive, manic type	24[a]	53/104 50.96%	23/101 22.77%	14/104 13.46%	9/101 8.91%
Lithium	Weisler et al., 2008	Bipolar I YMRS ≤12 MADRS ≤12 Acute current or recent manic, depressive, or mixed index episode treated with QUE	104	291/404 72.03%	102/364 28.02%	186/404 46.04%	66/364 18.13%

Olanzapine	Tohen et al., 2006	Bipolar I YMRS ≤12 HAM-D ≤8 2 prior mixed or manic episodes in past 6 years	48	44/136 32.35%	27/225 12%	53/136 38.97%	68/225 30.22%
Olanzapine	Vieta et al., accepted for publication	Bipolar I ≥2 mood episodes in the previous year		52/132 39.39%	19/130 14.61%	23/132 17.42%	12/130 9.23%
Olanzapine combined with lithium/divalproex	Tohen et al., 2004	Bipolar I YMRS ≤12 HRSD-21 ≤8	72	11/38 28.95%	6/30 20%	15/38 39.47%	7/30 23.33%
Oxcarbazepine combined with lithium	Vieta et al. (2008b)	Bipolar I or II YMRS ≤12 MADRS ≤20 No acute phases in 6 months	52	8/29 27.59%	4/26 15.38%	9/29 31.03%	3/26 11.54%
Quetiapine	Weisler et al., 2008	Bipolar I YMRS ≤12 MADRS ≤12 Acute current or recent manic, depressive, or mixed index episode treated with QUE	104	291/404 72.03%	121/404 29.95%	186/404 46.04%	65/404 16.09%
Quetiapine combined with lithium/divalproex	Suppes et al., 2009	Bipolar I YMRS ≤10 MADRS ≤13	104	61/313 19.49%	22/310 7.09%	102/313 32.59%	41/310 13.23%
Quetiapine combined with lithium/divalproex	Vieta et al. (2008a)	Bipolar I YMRS ≤12 HAM-D ≤12	104	96/367 26.16%	36/336 10.71%	84/367 22.89%	26/336 7.74%
Risperidone LAI	Quiroz et al., 2010	Bipolar I Recent manic/mixed episode or stable patients with ≥1 mood episode in past 4 months	96	62/135 45.93%	22/140 15.71%	14/135 10.37%	20/140 14.29%
Risperidone LAI	Vieta et al., accepted for publication	Bipolar I ≥2 mood episodes in the previous year		52/132 39.39%	26/131 19.84%	23/132 17.42%	25/131 19.08%
Risperidone LAI + treatment as Usual	Macfadden et al., 2009	Bipolar I ≥4 episodes in the past year	52	12/59 20.34%	5/65 7.69%	11/59 18.64%	8/65 12.31%
Valproate	Bowden et al., 2000	Bipolar I Manic episode ≤3 months before randomization. MRS ≤11 DSS ≤13 GAS >60, No suicidal risk	52	21/94 22.34%	33/187 17.65%	15/94 15.96%	12/187 6.42%
Ziprasidone combined with lithium/divalproex	Bowden et al., 2010	Bipolar I Curent or recent manic/mixed episode MRS ≥14	24	14/111 12.61%	7/127 5.51%	16/11 14.41%	16/127 12.60%

[a] NNT analyses refer to 12-month period.

1978). "Manic-prone" *vs.* "depressive-prone" patients were first analyzed in a clinical trial by Quitkin et al. (1986), and later in a community sample (Osher et al., 2000), while the first large sample was studied in STEP-BD project (Perlis et al., 1995). The concept of "predominant polarity" was operationalized and validated by Colom et al. (2006). Thus, a large body of evidence suggests that the predominance of polarity in bipolar disorder (BD), defined as at least twice as many episodes of one pole of the disorder over the other, is a valid prognostic parameter with important clinical and therapeutic implications (Colom et al., 2006; Rosa et al., 2008; Vieta et al., 2009). According to Colom et al., 2006, about one half of bipolar patients qualify for a specific predominant polarity. In European and American populations 50–60% of patients present predominant depressive polarity and about 40% have predominantly manic polarity (Tohen et al., 2009). Only in Israel a study by Osher et al. (2000) detected a predominately manic course of illness is more common and did not find any gender-related differences in type of illness course.

Marked clinical differences between predominantly manic and depressive bipolar patients, namely more frequent presence of substance misuse, psychotic symptoms, hospitalizations and cognitive impairment among patients with manic polarity (Colom et al., 2006; Martinez-Aran et al., 2007) and a higher number of suicide attempts, seasonal pattern and melancholic features in patients with predominantly depressive polarity (Goikolea et al., 2007; Rosa et al., 2008), justify the need of a differential treatment approach according to predominant polarity.

The current first-line treatment strategies for long term treatment of BD are represented by lithium, lamotrigine, valproate, olanzapine, quetiapine, aripiprazole, risperidone LAI (long-acting injectable formulation) and ziprasidone (Yatham et al., 2009). Whatsoever, implementing effective treatments for maintenance therapy of BD continues to represent a significant clinical challenge.

Number needed to treat (NNT), a measure of effect size, is a recommended tool for reporting results of clinical trials for BD (Gray, 2004; Martinez-Aran et al., 2008). NNT summarizes the effect of treatment in terms of the number of patients a clinician needs to treat with a particular therapy to get a real responder to the drug. Calculation of NNT can quantify the clinical relevance of a statistically significant study result (Citrome 2008).

The aim of the present study was to compare the efficacy profile of the drugs used for maintenance treatment of BD as regards to their potential to prevent depressive *versus* manic episodes. For this purpose we have introduced a metric named Polarity Index, a numeric expression of the efficacy profile of a given drug obtained from NNT for prevention of depressive episodes and NNT for mania prevention ratio.

2. Experimental procedures

Randomized controlled trials (RCTs) of medications used for the maintenance treatment of BD were systematically reviewed. A comprehensive Pubmed search of all English-language articles published up to June 2011 was performed. Terms 'bipolar disorder', 'mania', 'mixed', or 'bipolar depression', were cross-referenced with trial characteristics search phrases and generic names of medications (approved or non-approved by regulatory agencies for their use in BD).The search was supplemented by manually reviewing reference lists from the identified publications.

Eligibility criteria were represented by randomized and double blind trials and use of an mood stabilizer or antipsychotic drug alone or in combination with a mood stabilizing agent such as lithium or valproate, to treat adult patients with documented BD I or II, with a placebo comparator. Included RCTs assessed the effectiveness of drugs in the maintenance treatment of BD compared to placebo with a minimal duration of 24 weeks, in patients aged over 18. Exclusion criteria were a small sample size (meaning median sample inferior to 16.5 subjects in each group as suggested by Richy et al., 2004, a study sample not exclusively composed of bipolar patients and an absence of a placebo control group.

NNT was calculated by taking the reciprocals of the differences between the rates of the outcomes for two interventions. Polarity Index was retrieved by dividing NNT for prevention of depressive episodes and NNT for prevention of manic episodes. When more studies regarding a single agent were available data were combined using weighted mean.

A Polarity Index of 1.0 indicates equal efficacy of a drug in prevention of manic and depressive episodes. Drugs with a Polarity Index superior to 1.0 may have stronger antimanic *versus* antidepressant prophylactic properties, while those with Polarity Index inferior to 1.0 are more effective for preventing depressive episodes than the manic ones.

3. Results

Sixteen studies satisfied the inclusion criteria. The characteristics of the RCTs that were finally included, alongside the results as published in the original studies, are reported in Table 1. All studies had an acute treatment phase, followed by a double-blind, relapse-prevention (maintenance) treatment phase. Some of the RCTs used a three-arm design and thus could be used to make two comparisons each.

Table 2 provides NNTs for recurrence prevention of manic and depressive episodes and Polarity Index for agents recommended for long-term treatment of BD.

Predominantly Antimanic Polarity Index was found for risperidone LAI (PI = 12.09) (Macfadden et al., 2009; Quiroz et al., 2010; Vieta et al., accepted for publication) aripiprazole (PI = 4.38) (Keck et al., 2007; Marcus et al., 2011) and ziprasidone (Bowden et al., 2010) (PI = 3.91), followed by olanzapine (Tohen et al., 2006; Tohen et al., 2004; Vieta et al., accepted for publication) (PI = 2.98) and lithium (PI = 1.39) (Bowden et al., 2000; Bowden et al., 2003; Calabrese et al., 2003; Prien et al., 1973; Weisler et al., 2008).

Quetiapine has the closest to 1.0 Polarity Index among the agents assessed (PI = 1.14) (Suppes et al., 2009; Vieta et al. 2008a; Weisler et al., 2008), while lamotrigine (PI = 0.40) (Bowden et al., 2003; Calabrese et al., 2003), oxcarbazepine (PI = 0.62) (Vieta et al., 2008b) and valproate (Bowden et al., 2000) (PI = 0.49) have Predominantly Antidepressive Polarity Index.

Logarithmic distribution of Polarity Index for the assessed medicaments is depicted in Fig. 1.

4. Discussion

This study provides a new metric to measure the relative prophylactic efficacy of drugs used in bipolar disorder

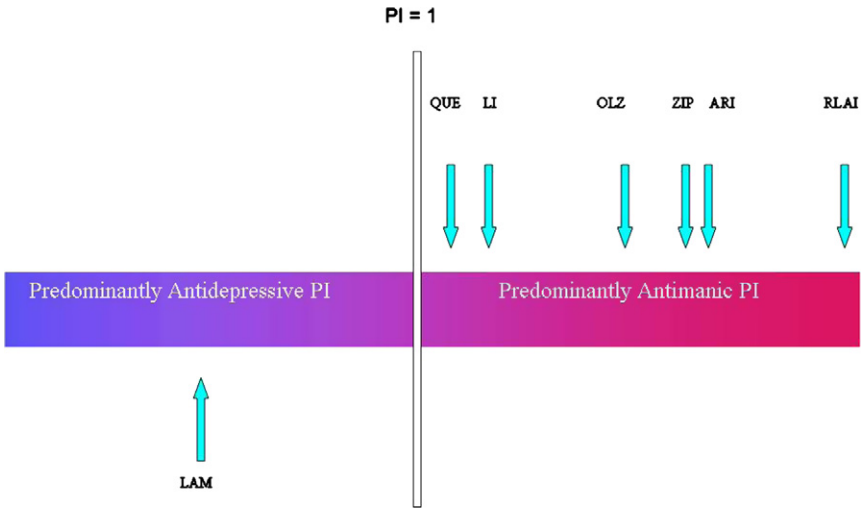
Table 2 Number needed to treat for prevention of manic and depressive episodes and Polarity Index for medicaments used in long-term treatment of bipolar disorder.

	NNT Mania	NNT Depression	Polarity Index
Aripiprazole-weighted mean Keck et al., 2007; Marcus et al., 2011	8.81	38.55	4.38
Aripiprazole monotherapy Keck et al., 2007	6.2	50	8.06
Aripiprazole combined with lithium/divalproex Marcus et al., 2011	10	33.3	3.33
Lamotrigine Bowden et al., 2003; Calabrese et al., 2003	50.4	20.2	0.40
Lithium Bowden et al., 2003; Calabrese et al., 2003; Weisler et al., 2008; Prien et al., 1973; Bowden et al., 2000	4.4	6.1	1.39
Olanzapine-weighted mean Tohen et al., 2004, Tohen et al., 2006; Vieta et al., accepted for publication	4.7	14	2.98
Olanzapine monotherapy Tohen et al., 2006; Vieta et al., accepted for publication	4.4	17.2	3.90
Olanzapine combined with lithium/divalproex Tohen et al., 2004	11.2	6.2	0.55
Oxcarbazepine Vieta et al., 2008b	8.2	5.1	0.62
Quetiapine-weighted mean Weisler et al., 2008; Vieta et al., 2008a; Suppes et al., 2009	3.5	4	1.14
Quetiapine combined with lithium/divalproex Vieta et al., 2008a; Suppes et al., 2009	7.1	5.9	0.83
Quetiapine monotherapy Weisler et al., 2008	2.4	3.3	1.38
Risperidone LAI Vieta et al., accepted for publication; Quiroz et al., 2010; Macfadden et al., 2009	4.4	53.2	12.09
Risperidone LAI monotherapy Vieta et al., accepted for publication; Quiroz et al., 2010	4	36.4	9.1
RLAI + treatment as usual Macfadden et al., 2009	7.9	15.8	2
Valproate Bowden et al., 2000	21.3	10.5	0.49
Ziprasidone Bowden et al., 2010	14.1	55.1	3.91

maintenance. It is also the first study aiming to determine the effectiveness profiles of the first-choice pharmacological treatment options for maintenance treatment of BD according to predominant polarity. As some patients are more prone to relapse into mania and others more prone to relapse into depression, the characterization of the polarity index of drugs used in maintenance treatment of BD appears clinically useful.

An emerging body of evidence indicates that predominance of episode polarity over the course of BD has been associated with treatment response and outcome of subsequent acute episodes (Vieta et al., 2009) and thus should be considered when determining the most appropriate therapeutical strategy for prophylaxis of BD.

According to the results, aripiprazole, risperidone LAI, ziprasidone and olanzapine have a high Polarity Index, indicating better mania-prevention than depression prevention properties. Likewise, lithium shows somewhat stronger antimanic than antidepressive properties, with a Polarity Index slightly superior to 1.0. Quetiapine has Polarity Index



LAM= lamotrigine, VPA= valproate, OXC= oxcarbazepine, QUE= quetiapine, LI= lithium, OLZ= olanzapine, ZIP= ziprasidone, ARI= aripiprazole, RLAI= risperidone long-acting injectable

Figure 1 Logarithmic distribution of Polarity Index for the agents used in maintenance treatment of Bipolar Disorder.

closest to 1.0, indicating its balanced, slightly stronger mania-recurrence preventing action. Among the drugs with Polarity Index inferior to 1.0, suggesting higher effectiveness in prevention of depressive episodes over manic and hypomanic ones, lamotrigine seems a valid therapeutic option for BD patients with predominant depressive recurrences. The Polarity Index for valproate and for oxcarbazepine appears to be lower than 1.0 but it should be interpreted with caution because the pivotal trials did not show statistical superiority of those two drugs over placebo. Data from negative or failed studies has been considered in this metric for drugs that have at least one positive maintenance trial, but for those drugs with no positive studies it makes little sense to speculate on their Polarity Index.

The present paper highlights the paucity of randomized placebo-controlled studies for maintenance treatment of BD. Given the scarcity of RCTs and in the interest of presenting most complete available data we have included both placebo-controlled trials assessing drugs in monotherapy and as combination therapies. Since the combination therapy trials were designed to assess the efficacy of drugs *vs.* placebo just like monotherapy trials and the baseline therapy is stratified and thus should not influence Polarity Index, mean Polarity Index for each drug was calculated from pooled data from all the published trials; Whatsoever, we have also reported Polarity Index values calculated separately for monotherapy *vs.* polytherapy studies, when available (see Table 2).

Randomized clinical trials for maintenance treatment of Bipolar Disorder are not only scarce; they are completely lacking for various agents. Carbamazepine is a clear example; although it was the first agent after lithium to be advocated for long-term treatment of BD and 2 lithium-controlled studies indicate drug's efficacy in relapse prevention (Greil et al., 1997; Hartong et al., 2003), by the time the research was conducted there were no available long-term placebo-controlled trials and thus Polarity Index of carbamazepine, could not be calculated. Future research needs to address the long-term effectiveness and the polarity index of agents such as carbamazepine, oxcarbazepine, valproate and newer antipsychotics such as paliperidone or asenapine.

The Polarity Index is a clinically useful measure, but has some limitations; it has been derived from clinical trial data and, therefore, issues related to trial design itself might have influenced the results. These issues include the abovementioned adjunctive *versus* monotherapy design as well as the index episode. Recent literature suggests that the polarity of the index episode tends to predict the polarity of relapse into a subsequent episode in a ratio of about 2:1 to 3:1 and influences response to treatment (Calabrese et al., 2004). A limitation of the present study is that most maintenance trials, from which Polarity Index was calculated, with few exceptions, enrolled enriched populations of patients who were currently or recently manic or mixed (see Table 1). Missing from most study designs was the recruitment of patients with index depressive episodes. Exclusion of depressed patients at enrollment may affect the polarity of mood episodes during the blinded relapse prevention phase since the study design was primarily configured to demonstrate efficacy in the delay or prevention of manic recurrence. The absence of depressive index episodes in a compound whose primary spectrum of efficacy is in depression, biases outcome against the drug, or *vice versa*; which reflects in Polarity Index calculation as well. However, the main reason why some compounds have only been studied in the context of index mania is their failure to separate from placebo in acute bipolar depression trials; hence, the bias against index depression is actually caused by the high polarity index of the drug, which makes it more suitable for the treatment of mania and the prevention of subsequent manic episodes, and for this reason we believe that the polarity index is still fully valid and informative. Hence, Polarity Index should be seen as a concept in continuous evolution, apace with the ongoing research. Although we have included all the available studies published up to date, future studies might influence Polarity Index values, especially for agents assessed in a small number of RCTs.

On a different matter, the Polarity Index does not say anything about the absolute efficacy of the drug, but about the efficacy profile (the higher the number, the more biased toward preventing mania as opposed to preventing depression). Polarity Index is a ratio, which does not provide information on NNT of each drug, but rather tells us how balanced a drug's action is. Clinicians should consider both of these concepts, NNT for preventing any mood episode (Popovic et al., 2011) and the Polarity Index, separately, when implementing a therapy; the NNT is a measure of the profile of a drug, which, along with drug tolerability, may help treatment choice in the context of personalized medicine.

This is not necessarily a limitation, but an issue to take into account. This metric may help, in the absence of a sufficient number of comparative long-term trials, to understand the relative efficacy profile of the drugs used in maintenance treatment of BD.

Overall, our findings indicate that anticonvulsants, and particularly lamotrigine, appear more effective for prevention of depressive episodes, while atypical antipsychotics and lithium may have a preponderant mania recurrence-preventing action. Interestingly, although not surprisingly, among the Second Generation Antipsychotics, Polarity Index seems to correlate with the affinity for dopamine type 2 (D2) receptors. Namely, aripiprazole (Ki = 0.4 nm), risperidone (Ki = 2.2 nm) and ziprasidone (Ki = 3.1 nm), drugs with most potent affinity for D2 receptors (Schatzberg and Nemeroff, 2009), have the highest Polarity Index, followed by olanzapine (Ki = 20 nm) and, finally, quetiapine (Ki = 180 nm). In fact, with the exception of aripiprazole, the affinity for D2 receptors directly correlates with Polarity Index. However, this may be due to the fact that aripiprazole is a partial agonist of D2 receptors, which in fact means that, despite a high D2 affinity, the dopamine blockade capacity may be inferior to that of drugs with slightly lower affinity for the D2 receptor, such as risperidone. The implications of this finding are that the Polarity Index may be influenced by the capacity of a given drug to reduce dopamine outflow in the brain, in the sense that the stronger the antidopaminergic action, the higher the Polarity Index and the greater the bias toward preventing mania rather than depression.

According to the British Association for Psychopharmacology guidelines (Goodwin 2009) different drugs should be prescribed according to the predominance of manic or depressive episodes. Since a patient with a predominant

depressive polarity is much more likely to relapse into a depressive episode, and therefore a suitable prophylaxis for that patient might be an agent that has been shown to have significant efficacy in preventing relapse of depressive episodes, such as lamotrigine. Similarly, a patient who has predominant manic polarity might require a stronger antimanic prophylactic agent, such as an atypical antipsychotic or lithium, in order to prevent further relapse of manic episodes. When combining drugs, it may be advisable to combine those which have different Polarity Index in order to have "complementary" efficacy profile, especially in patients who do not present a predominant polarity. On the whole, Polarity Index may be a useful aid for clinicians in the complex process of implementing maintenance therapy for bipolar disorder.

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Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

Professor Vieta has received research grants and served as consultant, advisor or speaker for the following companies: Almirall, Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer Inc., Sanofi-Aventis, Servier, Solvay, Schering-Plough, Takeda, United Biosource Corporation, and Wyeth, research funding from the Spanish Ministry of Science and Innovation, the Stanley Medical Research Institute and the 7th Framework Program of the European Union.

Professor González-Pinto has served as consultant, advisor or speaker for the following companies: Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, Pfizer Inc., Sanofi-Aventis, Shering-Plough, Boehringer-Ingelheim and Wyeth.

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3. POLARITY INDEX OF PSYCHOLOGICAL INTERVENTIONS IN MAINTENANCE TREATMENT OF BIPOLAR DISORDER (Objective 2)

3.1. Introduction

The current first-line treatment for the long term management of bipolar disorder is represented by pharmacological treatment (Yatham et al., 2009; Vieta et al, 2011). Whatsoever, far-from-satisfactory outcome even among medicated patients, with relapse rates ranging from 40-60% (Tohen et al., 2006; Tohen et al., 2003, Judd et al.,2008), has lead to develop several psychological interventions, aiming to delay recurrences, prevent relapses and reduce episode length, when combined with pharmacotherapy (Miklowitz, 2008, Schöttle et al.,2011).

The targets of different psychological interventions may vary, although the boundaries are blurry, and often address similar ingredients. Important differences exist as to the content and structure of various psychological interventions and up to date no attempt was made to classify interventions according to their ability to prevent manic vs. depressive episodes. The utility of such a classification is obvious when considering that around 50% of patients present with a marked predominant polarity

defined as at least twice as many episodes of one pole of the disorder over the other (Colom et al, 2006), which is one of the strongest predictors of relapse into a specific episode polarity (Baldessarini et al, 2012).

In bipolar disorder, benefits of an intervention, such as efficacy of a treatment in maintenance therapy, as emerging from the results of clinical trials, can be expressed in terms of Number Needed to Treat (NNT) (Martinez-Aran et al. 2008; Ketter et al., 2011; Popovic et al., 2011). NNT is a measure of effect size, and calculation of the NNT reflects the number of patients a clinician needs to treat with a particular therapy to expect to prevent one adverse event (Citrome, 2008).

Recently our group has developed the construct of "Polarity Index", a novel metric depicting the relative antimanic versus antidepressive preventive efficacy of an intervention in Bipolar Disorder maintenance treatment (Popovic et al., 2012). Polarity Index derives from NNT to prevent depressive episodes and NNT for prevention of mania ratio (Polarity Index = NNT depression prophylaxis / NNT mania prophylaxis). The aim of the present study is to calculate Polarity Index and rank the available

psychological interventions according to their efficacy profile by the means of Polarity Index.

3.2. Methods

A comprehensive literature search of all the articles published up to May 2012 incorporating results of searches of Medline and Pubmed was performed.

Search terms such as “bipolar disorder”, “mania”, “mixed episode”, or ‘bipolar depression’, were cross-referenced with “psychotherapy”, “psychological interventions”, “psychosocial interventions” and trial characteristics search phrases. The search was supplemented by manually reviewing reference lists from the identified publications.

We planned *a priori* the inclusion of studies meeting the following criteria: randomized controlled trials (RCTs) comparing efficacy of a psychological intervention versus a comparator group in bipolar disorder maintenance treatment in patients aged over 18. Exclusion criteria were a small sample size (median sample inferior to 16.5 subjects, as suggested by Richy et al., 2004), a study sample not exclusively composed of bipolar patients and the absence of a control group.

Thirty-four trials were identified, and ten met the inclusion criteria.

Names of authors, institutions or journals were not kept blind.

NNT, a measure of effect size that expresses the number of patients a clinician needs to treat with a particular therapy to expect to prevent one adverse event, was calculated by taking the reciprocals of the differences between the rates of the outcomes for two interventions (Citrome, 2008). NNT for prevention of relapse into any episode, mania and depression for each treatment assessed was calculated from the reports of all the studies that fulfilled the inclusion criteria.

Polarity Index is a metric indicating the relative antimanic versus antidepressive preventive efficacy of interventions. PI was retrieved by calculating NNT for prevention of depression and NNT for prevention of mania ratio, as emerging from the results of randomized placebo-controlled trials. PI value above 1.0 indicates relatively higher antimanic prophylactic properties, while a number below 1.0 indicates a relatively greater antidepressive action (Popovic et al., 2012).

3.3. Results

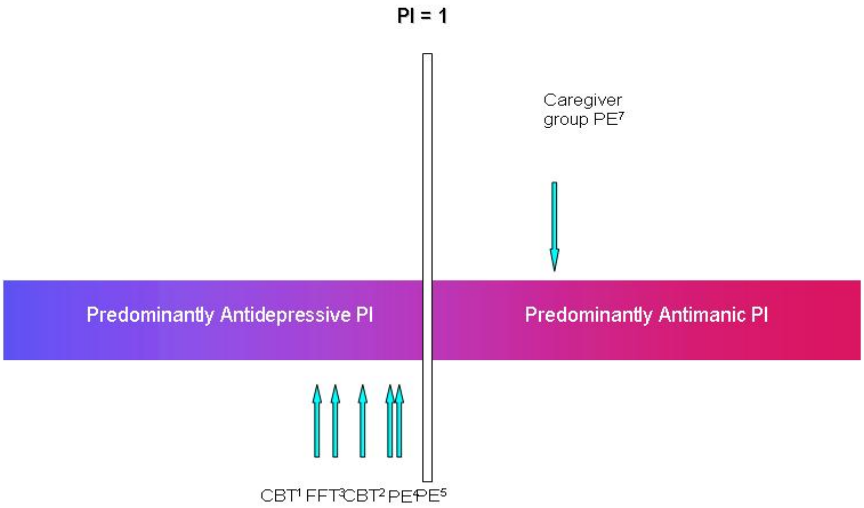
Ten studies satisfied the inclusion criteria, but it was possible to calculate Polarity Index for 9 of them. The characteristics of the RCTs that were finally included, alongside the results as published in the original studies, are reported in Table 1. Excluded trials, alongside with the reason of their exclusion, are shown in Table 2. Table 3 provides NNTs for recurrence prevention of manic, depressive and any mood episode alongside with Polarity Index for adjunctive psychotherapies in long-term treatment of bipolar disorder for all the RCTs where it was possible to calculate NNT, and thus Polarity Index.

Predominantly antidepressive Polarity Index was found for cognitive behavioural therapy, with values of 0.33 and 0.63 at 12 months and 30 months, respectively, in studies by Lam et al. (Lam et al., 2003; Lam et al., 2005); Polarity Index of 0.42 was found for family-focused therapy (Miklowitz et al., 2003). A predominantly antidepressive Polarity Index of 0.73 was found for psychoeducation after a 2-year follow-up (Colom et al., 2003), and 0.78 at 5-year follow-up (Colom et al., 2009).

Predominantly antimanic Polarity Index of 1.78 was found for caregiver group psychoeducation (Reinares et al., 2008).

Polarity Index of 1 found for enhanced relapse prevention (Lobban et al., 2010), 3.36 found for brief technique-driven interventions (Perry et al.,1999), and 0.89 for cognitive behavioural therapy in the study by Meyer and Hautzinger (2011) can not be considered as reliable since the trials were negative.

Logarithmic distribution of Polarity Index for the assessed interventions is depicted in the following figure:



PI= Polarity Index, CBT= cognitive behavioural therapy, FFT= family-focused therapy, PE= psychoeducation [1]Lam et al., 2003; [2]Lam et al., 2005; [3]Miklowitz 2003; , 2011; [4]Colom et al.,2003; [5]Colom et al., 2009;; [7]Reinares 2008

3.4. Discussion and Conclusions

This study applies Polarity Index, a novel metric developed to measure the relative prophylactic efficacy profile of medicaments in bipolar disorder, to all available psychological interventions. To the best of our knowledge, this is the first paper aiming to determine the efficacy profiles in relapse prevention of depressive vs. manic episodes of psychological treatments used as adjuvants to pharmacotherapy in maintenance treatment of bipolar disorder.

As some patients are more prone to relapse into mania and others more prone to relapse into depression, the characterization of the polarity index of psychotherapeutic interventions used in maintenance treatment of BD appears clinically useful.

According to the results that emerged, cognitive behavioural therapy, family-focused therapy and psychoeducation had Polarity Index below 1.0, indicating their more antidepressive than antimanic prophylactic effects, while caregiver group psychoeducation had Polarity Index above 1.0, indicating a prevalently antimanic action. Three studies, one cognitive behavioural therapy trial (Meyer and Hautzinger, 2011), enhanced relapse prevention (Lobban et al., 2010) and brief

technique-driven interventions (Perry et al.,1999), have Polarity Index of 0.89, 1 and 3.36, respectively, but can not be considered reliable since the NNT for prevention of any mood episode was not statistically significant, and the trials themselves were negative. Furthermore, Polarity Index could not be calculated for cognitive behavioural therapy by Scott et al. (2006), since not only was the NNT for prevention of any episode not significant, but NNT for prevention of depressive episodes could not be calculated because there was the same number of depressive relapses in the intervention group as in the control group. Numerous studies did not report relapse rates into mania and depression separately and thus we were unable to calculate their Polarity Index (See Table 2).

Interestingly, in both of the only two of the abovementioned trials that presented extended follow-up results (Lam et al.,2003, Lam et al.,2005, Colom et al.,2003, Colom et al.,2009) both interventions showed a trend in shifting towards PI of 1 over time, namely towards a more balanced action.

The implications of these results are multiple; above all PI may guide the clinician into deciding which intervention may be more indicated for a single patient. Comparably to pharmacological

interventions in bipolar disorder, or any kind of intervention in medicine for that matter, not all the interventions are equally suitable for each patient; thus Polarity Index may represent an useful tool to help the clinicians to select the most appropriate intervention for each patient in the era of personalized medicine.

This may be useful in treatment election suggesting that, for example, patients with predominant depressive polarity may benefit more from cognitive behavioural therapy, family-focused therapy or psychoeducation, while caregivers of patients with predominant manic polarity may be advised to undertake psychoeducation for caregivers. Moreover, combining patient psychotherapy and caregiver-oriented interventions may help achieve a more balanced, complementary, Polarity Index.

Future studies are needed in order to isolate the "active ingredients" responsible for therapeutic response and thus enable to design new, eventually shorter, interventions that would focus on the essential components in order to prevent episodes of different polarity. This study also evidences paucity of trials assessing long-term efficacy of adjunctive psychotherapeutic interventions. Above all, it underlines the scarcity of interventions efficacious for predominantly manic patients.

Interestingly, this is precisely the opposite situation as for drugs PI. Most available maintenance pharmacotherapies for bipolar disorder have PI above 1, meaning that they are better preventing mania than depression (Popovic et al, 2012). Psychological interventions appear better to prevent depression than mania, with the exception of those with more educational components or working through relatives, who may be particularly motivated or skilled to prevent mania, rather than depression. Interventions based on patient participation or with more cognitive and face-to-face participation may be more effective preventing depression. The main limitation (and strength!) of the Polarity Index is the fact that it derives from RCT data, meaning that issues related to trial design may influence Polarity Index calculations. Among these, issues such as a lack of definition of "placebo comparator" for psychological interventions and uneven number or sessions (or even comparison of an adjunctive intervention to "Treatment As Usual" as control comparator), not only between different interventions, but also among the experimental and control intervention in the same study are evident. The medicaments that patients were assuming differ, and were often not specified. Study samples were extremely heterogeneous (as may be seen

from “trial characteristics” column in Table 1); several trials included patients with Bipolar I or both Bipolar I and II diagnosis, euthymic or acute patients. Even the definition of “euthymia” (syndromic or symptomic) was not always uniform, as well as the required duration of euthymia. Differences in exclusion criteria, such as the number of previous episodes and presence of comorbid pathologies are also common between studies. Furthermore the used scales and outcome measures are highly heterogeneous. Above all, the name of intervention (e.g. cognitive behavioural therapy) does not necessarily mean that same treatment protocol was applied; reason why, unlike the Polarity Index for drugs, we were unable to pool data when more studies were available for one intervention.

The Polarity Index does not say anything about the absolute efficacy of the intervention, but about the efficacy profile (the higher the number, the more biased toward preventing mania as opposed to preventing depression). It is a ratio, which does not provide information on NNT of each drug, but rather tells us how balanced an intervention is. Both of these concepts, NNT and the Polarity Index, need to be considered separately, NNT to

determine the efficacy of an intervention, and Polarity Index to depict its profile.

Polarity Index may guide treatment choice in the context of personalized patient care, not only for pharmacological treatments but also, and maybe even more so, given the lack of any similar tools, for adjunctive psychotherapeutic interventions. The fact that the PI of most pharmacotherapies and psychotherapies may be complementary should promote combinations of the two. This metric may help, in the absence of a sufficient number of comparative long-term trials, to understand the relative efficacy profile of adjunctive psychological interventions used in maintenance treatment of BD and perhaps design interventions with specific profiles.

4. CLINICAL IMPLICATIONS OF PREDOMINANT POLARITY AND THE POLARITY INDEX OF DRUGS USED IN MAINTENANCE TREATMENT OF BIPOLAR DISORDER: A NATURALISTIC STUDY (Objective 3)

4.1. Introduction

The aim of the present study was to apply Polarity Index to real-world setting. Secondary aim of this naturalistic study was to ally Polarity Index in order to assess eventual differences between predominantly manic and depressed patients, with a special focus on their pharmacological treatment.

On these grounds we have calculated mean Polarity Index for current pharmacological treatment of 604 patients enrolled in Bipolar Disorders Program of the Hospital Clinic and University of Barcelona. The abovementioned program delivers evidence-based treatment for patients with bipolar disorder in the context of a specialized setting (Vieta, 2011a; Vieta, 2011b; Rosa et al, 2011).

The objective was to test whether clinicians were actually applying the concept of PI to their patients. Theoretically, patients with MPP would be receiving treatments with higher PI

than patients with DPP. Since combination drug regimens are ubiquitous in clinical practice (Goldberg et al., 2009; Tamayo et al., 2010), Polarity Index was calculated as a mean of Polarity Index of all the prescribed drugs in each patient.

4.2. Methods

Depressive predominant polarity (DPP) was defined as at least two-thirds of a patient's past episodes fulfilling DSM-IV criteria for Major Depressive Episode.

Manic or hypomanic predominant polarity (MPP) was defined as at least two thirds of past episodes fulfilling DSM-IV criteria for manic or hypomanic episodes (Colom et al., 2006). Mixed episodes were counted for as well but were not considered as a part of Depressive Polarity or Manic Polarity. The patients that did not meet criteria for either predominant polarity were excluded from the analysis.

Polarity Index, a metric indicating antimanic and antidepressive prophylactic potential of drugs, was retrieved by calculating NNT for prevention of depression and NNT for prevention of mania ratio (Popovic et al., 2012), as emerging from the results of randomized placebo-controlled trials (Table

4). NNTs were calculated as weighted mean from the results of all published studies that satisfied the following inclusion criteria: randomized and double blind studies, with a minimal duration of 24 weeks, assessing effectiveness of a mood stabilizer or an antipsychotic drug alone or in combination with a mood stabilizing agent versus a placebo comparator as maintenance treatment in patients affected by Bipolar Disorder type I or II and aged ≥ 18 (Popovic et al., 2011).

A Polarity Index of 1 indicates equal efficacy of a drug in prevention of manic and depressive episodes. Drugs with a Polarity Index superior to 1 may have stronger antimanic versus antidepressant prophylactic properties, while those with Polarity Index inferior to 1 are more effective for preventing depressive episodes than the manic ones.

Polarity Index was calculated for current treatment of each patient. When patients received more than 1 pharmacological treatment Polarity Index was calculated as mean of all the prescribed treatments; e.g. Polarity Index of patient treated with Lithium and Lamotrigine is calculated as following:

[1.52 (Polarity Index Lithium) + 0.74 (Polarity Index Lamotrigine)] / 2 (number of drugs) = 1.13]

Polarity Index of 1.13 suggests a balanced, slightly more antimanic than antidepressive profile of the drug regimen.

Study Sample

The study sample is composed of 604 consecutive patients enrolled in the systematic prospective naturalistic follow-up study of the Bipolar Disorders Program of the Hospital Clinic and University of Barcelona, a tertiary center providing integrated care for patients from a specific catchment area as well as difficult-to-treat bipolar patients derived from all over Spain, ongoing from 1994 up to date, as already described elsewhere (Colom et al., 2006; Nivoli et al., 2011). The systematic prospective follow-up was approved by the Ethical and Research Committee of the Hospital University Clinic.

Patients' clinical and sociodemographic data were systematically collected on bimonthly bases. Eligibility criteria were represented by age ≥18, fulfilling DSM-IV TR criteria for Bipolar I or II Disorder and providing written informed consent.

Data collection

Psychiatric diagnoses were formulated by senior psychiatrists according to DSM-IV-TR criteria and confirmed by Structured Clinical Interview for DSM-III-R-axis I (SCID-I) and axis II-

SCID-I and SCID-II (Spitzer et al., 1990). Episodes were prospectively assessed through DSM-IV check list for mania, hypomania, mixed episodes or depression. Clinical variables, such as number and polarity of previous episodes, number of hospitalizations, age at onset, age of first hospitalization, polarity of first episode, history of psychosis and suicidal behavior, were obtained from the structured interviews with patients and their relatives. Several more variables were specifically assessed; namely: demographic data, medical and psychiatric comorbidities, and psychiatric history of first-degree relatives, seasonality and rapid cycling (according to DSM-IV criteria), while information regarding social and occupational functioning and presence of life-events related to illness onset were assessed by the means of the Holmes and Rahe inventory (Holmes and Rahe, 1967).

Patients were divided into two groups on the basis of the type of Predominant Polarity: DPP and MPP. The two groups were compared regarding clinical and sociodemographic variables as well as regarding Polarity Index, which was calculated for current pharmacological treatment of each patient.

Statistical Analyses

Descriptive analyses were utilized for the definition of the frequencies. Continuous variables were compared by Student's t-tests and ANOVA and categorical variables by Pearson Chi-square with Yates' correction and Fisher's exact test for the comparison of categorical data (α value, two tailed). Mean differences in quantitative variables with a non-normal distribution were assessed by Mann-Whitney U test for independent variables. Given the exploratory nature of our study we did not apply corrections for multiple comparisons, and alpha level was set at the .05 level (2-tailed). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, 18.0 version for Windows).

4.3. Results

Three hundred forty-seven patients (57.45 %) out of the first consecutive 604 patients screened were excluded from the analyses since they did not present a specific predominant polarity according to the definition by Colom et al. (2006).The mean duration of follow-up for our sample was 10.4 years (SD=4.97). Two hundred fifty-seven patients (n=257, 52.55 %) fulfilled the inclusion criteria. One hundred forty-three patients

(n=143, 55.6 %) were classified as Depressive Polarity, whilst one hundred fourteen (n=114, 44.4 %) patients fulfilled criteria for Manic Polarity.

Demographic characteristics, global social functioning variables and clinical qualitative features are shown in Table 5.

Regarding demographic and global social functioning variables, MPP and DPP groups presented with only one significant difference (gender); hence, male patients were more likely to have MPP. As to the distinguishing clinical features, the MPP group presented significantly with higher prevalence of Bipolar Disorder I diagnosis, substance use prior to the illness onset and more psychotic symptoms (lifetime and at onset) than the DPP group. In contrast, Depressive Polarity group was strongly associated with Bipolar II diagnosis, depressive onset, presence of life events preceding first episode, the presence of melancholia and suicide attempts rate.

Differential quantitative features between MPP and DPP groups are shown in Table 6. MPP patients presented with younger age, younger age at onset and younger age at first hospitalization, more hospitalizations as well as more manic and hypomanic episodes. Depressive episodes were more frequent in the DPP

group, whilst no difference was detected between the two groups regarding total number of episodes, number of mixed episodes nor number of suicide attempts.

Table 7 provides the Polarity Index reflecting current pharmacological treatment of the two groups. Total Polarity Index (calculated as mean value of Polarity Index of all prescribed antipsychotics and mood stabilizers in each patient), as well as Polarity Index of antipsychotics and mood stabilizers taken separately, were higher, indicating a stronger antimanic regimen, in the MPP group.

Table 8 summarizes the current pharmacological treatment of Manic Polarity and Depressive Polarity patients. When analyzing single drugs, the prescription of First Generation Antipsychotics and Second Generation Antipsychotics Olanzapine and Risperidone was significantly more frequent among MPP patients, whilst use of Lamotrigine, Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs) and Benzodiazepines was more prevalent amongst DPP patients. Interestingly, lithium showed a trend for higher prescription rate

in the Manic Polarity group, but without reaching statistical significance (χ^2=3.521, p=0.061).

4.4. Discussion

The present study aimed to apply Polarity Index, a novelmetric aiming to help clinicians to understand the prophylactic efficacy profile of drugs used for treatment of Bipolar Disorder, to real-world clinical practice.

The results of the present study confirm that, in clinical settings, the maintenance treatment of Bipolar Disorder is in accordance with the results emerging from data retrieved from randomized clinical trials by calculating NNT for prevention of depression vs. mania ratio; namely, patients with MPP presented significantly higher Polarity Index, indicating that clinicians chose a treatment regimen with stronger antimanic prophylactic action, than for DPP patients. The same was true for Polarity Index of Atypical Antipsychotics and Polarity Index of Mood Stabilizers when analysed separately. When examining the prevalence of prescription of single mood stabilizing drugs, lamotrigine was prescribed more frequently in patients with DPP, alongside with most antidepressants (TCAs, SSRI and SNRIs) and

benzodiazepines. In comparison, Risperidone, Olanzapine and Neuroleptics were prescribed more often in the MPP group.

In addition to different pharmacological treatment, several clinical differences were detected between the groups. The present study confirms most of the findings reported by Colom et al. (2006). Main differences, probably due to a larger study sample, involved gender, history of psychotic symptoms, substance use preceding first episode and seasonal pattern. Other findings were consistent, as expected with data from our group (Nivoli et al 2011; Undurraga et al, 2011) but also from independent samples from other areas, countries, and continents (Rosa et al, 2008; Mazzarini et al, 2009;González-Pinto et al, 2010; Baldessarini et al, 2012).

In summary, MPP was associated with male gender, younger age, younger age at illness onset, younger age of first hospitalization, higher hospitalization rate, more manic and hypomanic episodes. Regarding clinical features, MPP was associated with Bipolar Disorder I primary substance abuse and psychotic symptoms. Factors associated with DPP were Bipolar Disorder II, depressive onset, more depressive episodes, stressful events preceding illness onset, more suicide attempts and melancholic features.

These data are mostly in accordance with recently reported findings by Baldessarini et al., (2012), who detected that Predominant Depression was associated with depressive or mixed onset, more mixed-states, and higher suicidal risk and that Predominant Mania was associated with initial mania or psychosis and more family history.

4.5. Limitations

Limitations of the present study include the tertiary-centre nature of the Barcelona Bipolar Program at Hospital Clinic, which includes a high percentage of difficult-to-treat patients, as well as issues regarding Polarity Index metric. Id est, Polarity Index could not be calculated for all drugs used in treatment of Bipolar Disorder since long-term trials were not conduced for all the agents. In some cases, as for Valproate and Oxcarbazepine, Polarity Index may not be reliable due to the failure to separate from placebo during the pivotal maintenance treatment studies, thus we have excluded them from the analysis. Polarity Index was retrieved from results of clinical trials, thus issues related to trial design itself (adjunctive versus monotherapy design, enrollment of enriched populations of patients who were mainly

currently or recently manic or mixed) may have biased the results as discussed in the primary paper on Polarity Index (Popovic et al., 2012).An interesting issue is that most maintenance trials assessed samples enriched for efficacy; however, lamotrigine trials were unique in sense that they included study sample enriched for tolerability, and not efficacy, which may have accounted for to the high NNT detected for lamotrigine (50.4 for mania prevention and 20.2 for prevention of depression) (Popovic et al., 2011; Bowden et al., 2003; Calabrese et al., 2003). It is important to remember that Polarity Index is not a measure of the absolute efficacy of a drug, like NNT, but it rather describes the drug profile; in the case of lamotrigine, although the trial design may have influenced the efficacy reflected in NNT calculation, it is not reflected in Polarity Index which, with the value of 0.40, indicates that lamotrigine is more antidepressant than antimanic.

4.6. Conclusions

Predominant polarity, proposed as a course specifier of particular relevance for long-term therapeutic decision-making process and outcome predictor (Tohen et al., 2009) in DSM-V (Colom and

Vieta, 2009), finds its clinical expression in Polarity Index. The present study not only provides further evidence to the importance of considering patients' predominant polarity, but also examines the actual use of the Polarity Index in routine clinical practice.

The results of the present naturalistic study confirm the usefulness of Polarity Index metric in maintenance treatment of BD. Important clinical differences between predominantly manic and predominantly depressed patients emerged, and justify the need for differentiated therapeutic approach in the two groups.

Our study shows that the treatment of patients with MPP was oriented mostly towards mania prevention, as evidenced by higher Polarity Index, while treatment of DPP patients was characterized by lower mean Polarity Index, thus directed towards preventing depression. Likewise, the choice of the specific drug, even within the same class, varied in accordance with patients' predominant polarity- Second Generation Antipsychotics with stronger antimanic vs. antidepressant properties were prescribed more often in the Manic Polarity group, and vice versa, mood stabilizers with lower Polarity Index were prescribed more frequently in Depressive Polarity patients.

Assuming that specialized care centres may provide higher standards of care and better outcomes than non-specialized settings (Kessing et al, in press), the Polarity index may be helpful as a tool to assess the quality of maintenance prescription for bipolar patients; hence, if MPP patients receive higher PI regimens than DPP patients, the treatment is likely to be evidence based.

5. GENERAL DISCUSSION

Due to the episodic and chronic nature of the illness, maintenance therapy is a critical part of treatment for bipolar disorder. The ultimate goal of treatment is the prevention of episode recurrence through the long-term management of the symptoms (Thase, 2008).

Scientific evidence concerning the treatment of affective disorders is even more complex given the low reliability and validity of diagnosis, as well as for the fact that a specific and different treatment needs to be considered separately for manic, hypomanic, mixed, and depressive episodes. Even drugs proven effective for the acute phase of either pole in each patient are often not adequate in the maintenance phase (Fountoulakis et al., 2012).

The main aims of this dissertation are to introduce a clinician-friendly metric that would enable to compare the efficacy profiles of the drugs and of adjunctive psychological interventions used for maintenance treatment of bipolar disorder as regards to their potential to prevent depressive versus manic episodes. Subsequently, Polarity Index metric was to be applied to real-world setting, in a naturalistic study, to a large sample of bipolar

patients, in order to assess the external validity of the metric.

The secondary aim was to ally Polarity Index in order assess eventual differences between predominantly manic and predominantly depressed patients, with a special focus on their pharmacological treatment.

NNT is a useful and meaningful concept for practicing clinicians which may help to translate the results of randomized controlled clinical trials to evidence-based medicine (Martinez-Aran et al., 2008). Nonetheless, most of the published studies have not reported NNT values for assessed medicaments.

NNT analysis evidenced differences in efficacy profiles among various agents used as first-line maintenance treatment for bipolar disorder. In general, our findings are in agreement with the recommendations of recent guidelines for the maintenance therapy of bipolar disorder (Yatham et al. 2009). Aripiprazole, olanzapine, quetiapine, risperidone LAI, ziprasidone, lithium, lamotrigine, and valproate have single-digit NNTs and are significantly effective for the prevention of any mood episode, but show substantial differences as to their ability to prevent mania and depression separately. Among the agents assessed, the only exception is given by oxcarbazepine combined with lithium

that had a significant single-digit NNT for prevention of any episode, mania, and depression, but CI did not result significant, probably for the lack of power due to the relatively small sample size.

The NNT analyses confirmed the efficacy of quetiapine (in monotherapy and combined with mood stabilizer), lithium, risperidone LAI, aripiprazole, and olanzapine in preventing manic recurrences. Lamotrigine, lithium, and quetiapine alone and combined with lithium/valproate presented significant NNTs for the prevention of depressive relapses. The data emerging from our analysis provide utter evidence that the treatments assessed differentiated in terms of whether they primarily prevent mania or depression or have bidirectional effects. The clinical relevance of the directional efficacy of the various medications is heightened in the context of predominant polarity, a parameter correlated with treatment response and outcome of later acute episodes (Vieta et al. 2009; Colom et al. 2006); nevertheless, placebo-controlled randomized clinical trials assessing long-term effectiveness of mood stabilizers and antipsychotics are surprisingly sparse, and important questions remain unanswered.

An apparent paradox emerges from NNT values analyses.

Namely, it may seem surprising that NNT for the prevention of any mood episode is often smaller than NNT for the prevention of manic or depressive relapses separately; however, one should bear in mind that the included studies were designed to assess efficacy in terms of prevention of any mood episode as primary aim.

The following step was to introduce a metric indicative of relative prophylactic efficacy of drugs used in bipolar disorder maintenance. It is also the first study aiming to determine the effectiveness profiles of the first-choice pharmacological treatment options for maintenance treatment of bipolar disorder according to predominant polarity (Popovic et al., 2012). As some patients are more prone to relapse into mania and others more prone to relapse into depression, the characterization of the Polarity Index of drugs used in maintenance treatment of bipolar disorder appears clinically useful.

An emerging body of evidence indicates that predominance of episode polarity over the course of bipolar disorder has been associated with treatment response and outcome of subsequent acute episodes (Vieta et al., 2009) and thus should be considered when determining the most appropriate therapeutical strategy for

prophylaxis of bipolar disorder.

According to the results, aripiprazole, risperidone LAI, ziprasidone and olanzapine have a high Polarity Index, indicats better mania prevention than prevention of depressive episodes. Likewise, lithium shows somewhat stronger antimanic than antidepressive properties, with a Polarity Index slightly superior to 1.0. Quetiapine has Polarity Index closest to 1.0, indicating its balanced, slightly stronger mania-recurrence preventing action. Among the drugs with Polarity Index inferior to 1.0, suggesting higher effectiveness in prevention of depressive episodes over manic and hypomanic ones, lamotrigine seems a valid therapeutic option for bipolar disorder patients with predominant depressive recurrences. The Polarity Index for valproate and for oxcarbazepine appears to be lower than 1.0 but it should be interpreted with caution because the pivotal trials did not show statistical superiority of those two drugs over placebo. Data from negative or failed studies has been considered in this metric for drugs that have at least one positive maintenance trial, but for those drugs with no positive studies it makes little sense to speculate on their Polarity Index.

The present dissertation highlights the paucity of randomized

placebo-controlled studies for maintenance treatment of bipolar disorder. Given the scarcity of RCTs and in the interest of presenting most complete available data we have included both placebo-controlled trials assessing drugs in monotherapy and as combination therapies. Since the combination therapy trials were designed to assess the efficacy of drugs vs. placebo just like monotherapy trials and the baseline therapy is stratified and thus should not influence Polarity Index, mean Polarity Index for each drug was calculated from pooled data from all the published trials; Whatsoever, we have also reported Polarity Index values calculated separately for monotherapy vs. polytherapy studies, when available (Table 9).

On a different matter, the Polarity Index does not say anything about the absolute efficacy of the drug, but about the efficacy profile (the higher the number, the more biased toward preventing mania as opposed to preventing depression).

Polarity Index is a ratio, which does not provide information on NNT of each drug, but rather tells us how balanced a drug's action is. Clinicians should consider both of these concepts, NNT for preventing any mood episode (Popovic et al., 2011) and the Polarity Index, separately, when implementing a therapy; the

NNT is a measure of the profile of a drug, which, along with drug tolerability, may help treatment choice in the context of personalized medicine. This is not necessarily a limitation, but an issue to take into account. This metric may help, in the absence of a sufficient number of comparative long-term trials, to understand the relative efficacy profile of the drugs used in maintenance treatment of bipolar disorder.

Overall, our findings indicate that anticonvulsants, and particularly lamotrigine, appear more effective for prevention of depressive episodes, while atypical antipsychotics and lithium may have a preponderant mania recurrence preventing action. Interestingly, although not surprisingly, among the Second Generation Antipsychotics, Polarity Index seems to correlate with the affinity for dopamine type 2 (D2) receptors. Namely, aripiprazole (Ki=0.4 nm), risperidone (Ki=2.2 nm) and ziprasidone (Ki=3.1 nm), drugs with most potent affinity for D2 receptors (Schatzberg and Nemeroff, 2009), have the highest Polarity Index, followed by olanzapine (Ki=20 nm) and, finally, quetiapine (Ki=180 nm). In fact, with the exception of aripiprazole, the affinity for D2 receptors directly correlates with Polarity Index. However, this may be due to the fact that

aripiprazole is a partial agonist of D2 receptors, which in fact means that, despite a high D2 affinity, the dopamine blockade capacity may be inferior to that of drugs with slightly lower affinity for the D2 receptor, such as risperidone. The implications of this finding are that the Polarity Index may be influenced by the capacity of a given drug to reduce dopamine outflow in the brain, in the sense that the stronger the antidopaminergic action, the higher the Polarity Index and the greater the bias toward preventing mania rather than depression.

According to the British Association for Psychopharmacology guidelines (Goodwin 2009) different drugs should be prescribed according to the predominance of manic or depressive episodes. Since a patient with a predominant depressive polarity is much more likely to relapse into a depressive episode, and therefore a suitable prophylaxis for that patient might be an agent that has been shown to have significant efficacy in preventing relapse of depressive episodes, such as lamotrigine. Similarly, a patient who has predominant manic polarity might require a stronger antimanic prophylactic agent, such as an atypical antipsychotic or lithium, in order to prevent further relapse of manic episodes.

When combining drugs, it may be advisable to combine those

which have different Polarity Index in order to have "complementary" efficacy profile, especially in patients who do not present a predominant polarity. On the whole, Polarity Index may be a useful aid for clinicians in the complex process of implementing maintenance therapy for bipolar disorder.

Polarity Index was also calculated for all the available adjunctive psychological interventions to measure their relative prophylactic efficacy profile in patients with bipolar disorder. To the best of our knowledge, this is the first study aiming to determine the efficacy profiles in relapse prevention of depressive vs. manic episodes of psychological treatments used as adjuvants to pharmacotherapy in maintenance treatment of bipolar disorder.

As some patients are more prone to relapse into mania and others more prone to relapse into depression, also the characterization of the Polarity Index of psychotherapeutic interventions used in maintenance treatment of bipolar disorder appears clinically useful.

According to the results that emerged, cognitive behavioural therapy, family-focused therapy and psychoeducation had Polarity Index below 1.0, indicating their more antidepressive than antimanic prophylactic effects, while caregiver group

psychoeducation had Polarity Index above 1.0, indicating a prevalently antimanic action. Three studies, one cognitive behavioural therapy trial (Meyer and Hautzinger, 2011), enhanced relapse prevention (Lobban et al., 2010) and brief technique-driven interventions (Perry et al.,1999), have Polarity Index of 0.89, 1 and 3.36, respectively, but can not be considered reliable since the NNT for prevention of any mood episode was not statistically significant, and the trials themselves were negative. Furthermore, Polarity Index could not be calculated for cognitive behavioural therapy by Scott et al. (2006), since not only was the NNT for prevention of any episode not significant, but NNT for prevention of depressive episodes could not be calculated because there was the same number of depressive relapses in the intervention group as in the control group. Numerous studies did not report relapse rates into mania and depression separately and thus we were unable to calculate their Polarity Index (See Table 2).

Interestingly, in both of the only two of the abovementioned trials that presented extended follow-up results (Lam et al., 2003, Lam et al., 2005, Colom et al., 2003, Colom et al., 2009) both interventions showed a trend in shifting towards PI of 1 over

time, namely towards a more balanced action.

The implications of these results are multiple; above all PI may guide the clinician into deciding which intervention may be more indicated for a single patient. Comparably to pharmacological interventions in bipolar disorder, or any kind of intervention in medicine for that matter, not all the interventions are equally suitable for each patient; thus Polarity Index may represent an useful tool to help the clinicians to select the most appropriate intervention for each patient in the era of personalized medicine.

This may be useful in treatment election suggesting that, for example, patients with predominant depressive polarity may benefit more from cognitive behavioural therapy, family-focused therapy or psychoeducation, while caregivers of patients with predominant manic polarity may be advised to undertake psychoeducation for caregivers. Moreover, combining patient psychotherapy and caregiver-oriented interventions may help achieve a more balanced, complementary, Polarity Index.

Future studies are needed in order to isolate the “active ingredients” responsible for therapeutic response and thus enable to design new, eventually shorter, interventions that would focus on the essential components in order to prevent episodes of

different polarity. This study also evidences paucity of trials assessing long-term efficacy of adjunctive psychotherapeutic interventions. Above all, it underlines the scarcity of interventions efficacious for predominantly manic patients. Interestingly, this is precisely the opposite situation as for drugs Polarity Index. Most available maintenance pharmacotherapies for bipolar disorder have Polarity Index above 1, meaning that they are better preventing mania than depression (Popovic et al, 2012). Psychological interventions appear better to prevent depression than mania, with the exception of those with more educational components or working through relatives, who may be particularly motivated or skilled to prevent mania, rather than depression. Interventions based on patient participation or with more cognitive and face-to-face participation may be more effective preventing depression.

This study applies Polarity Index, a novel metric developed to measure the relative prophylactic efficacy profile of medicaments in bipolar disorder, to all available psychological interventions. To the best of our knowledge, this is the first attempt to determine the efficacy profiles in relapse prevention of depressive vs. manic episodes of psychological treatments used

as adjuvants to pharmacotherapy in maintenance treatment of bipolar disorder.

According to the results that emerged, cognitive behavioural therapy, family-focused therapy and psychoeducation had Polarity Index below 1.0, indicating their more antidepressive than antimanic prophylactic effects, while caregiver group psychoeducation had Polarity Index above 1.0, indicating a prevalently antimanic action. Three studies, one cognitive behavioural therapy trial (Meyer and Hautzinger, 2011), enhanced relapse prevention (Lobban et al., 2010) and brief technique-driven interventions (Perry et al.,1999), have Polarity Index of 0.89, 1 and 3.36, respectively, but can not be considered reliable since the NNT for prevention of any mood episode was not statistically significant, and the trials themselves were negative. Furthermore, Polarity Index could not be calculated for cognitive behavioural therapy by Scott et al. (2006), since not only was the NNT for prevention of any episode not significant, but NNT for prevention of depressive episodes could not be calculated because there was the same number of depressive relapses in the intervention group as in the control group. Numerous studies did not report relapse rates into mania and

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Polarity Index may guide treatment choice in the context of personalized patient care, not only for pharmacological treatments but also, and maybe even more so, given the lack of any similar tools, for adjunctive psychotherapeutic interventions. The fact that the PI of most pharmacotherapies and

psychotherapies may be complementary may encourage the combination of the two. This metric may help, in the absence of a sufficient number of comparative long-term trials, to understand the relative efficacy profile of adjunctive psychological interventions used in maintenance treatment of bipolar disorder and perhaps design interventions with specific profiles.

The final phase of this study consisted in applying Polarity Index to real-world clinical practice.

The results of this naturalistic study confirm that, in clinical settings, the maintenance treatment of bipolar disorder is in accordance with the results emerging from data retrieved from randomized clinical trials by calculating NNT for prevention of depression vs. mania ratio; namely, patients with MPP presented significantly higher Polarity Index, indicating that clinicians chose a treatment regimen with stronger antimanic prophylactic action, than for DPP patients. The same was true for Polarity Index of Atypical Antipsychotics and Polarity Index of Mood Stabilizers when analyzed separately. When examining the prevalence of prescription of single mood stabilizing drugs, lamotrigine was prescribed more frequently in patients with DPP, alongside with most antidepressants (TCAs, SSRI and SNRIs)

and benzodiazepines. In comparison, Risperidone, Olanzapine and Atypical antipsychotics were prescribed more often in the MPP group.

In addition to different pharmacological treatment, several clinical differences were detected between the groups. The present study confirms most of the findings reported by Colom et al. (2006). Main differences, probably due to a larger study sample, involved gender, history of psychotic symptoms, substance use preceding first episode and seasonal pattern. Other findings were consistent, as expected with data from our group (Nivoli et al 2011; Undurraga et al, 2011) but also from independent samples from other areas, countries, and continents (Rosa et al, 2008; Mazzarini et al, 2009;González-Pinto et al, 2010; Baldessarini et al, 2012).

In summary, MPP was associated with male gender, younger age, younger age at illness onset, younger age of first hospitalization, higher hospitalization rate, more manic and hypomanic episodes. Regarding clinical features, MPP was associated with Bipolar Disorder I primary substance abuse and psychotic symptoms. Factors associated with DPP were Bipolar Disorder II, depressive onset, more depressive episodes, stressful events preceding

illness onset, more suicide attempts and melancholic features. These data are mostly in accordance with recently reported findings by Baldessarini et al., (2012), who detected that Predominant Depression was associated with depressive or mixed onset, more mixed-states, and higher suicidal risk and that Predominant Mania was associated with initial mania or psychosis and more family history.

6. LIMITATIONS

The first limitation of the NNT calculation is that, in order to present the most complete data available, we have included both RCTs assessing drugs in monotherapy as well as combined with mood stabilizers such as lithium and valproate. The studies were not completely homogeneous with respect to clinical characteristics of the sample (rapid-cycling course, manic/mixed states or depression, refractory patients or unbiased samples), sample size, and rates of study completion, which may compromise to some extent the generalizability of reported NNTs.

Number needed to harm analysis went beyond the scopes of this study, although medication selection is based on tolerability as well as efficacy.

NNTs for the prevention of mixed episodes were omitted since most available RCTs have not proceeded to such assessment and the number of events in the trials that did look at it was extremely small.

The limitations of Polarity Index are that it has been derived from clinical trial data and, therefore, issues related to trial design

itself might have influenced the results. These issues include the abovementioned adjunctive versus monotherapy design as well as the index episode. Recent literature suggests that the polarity of the index episode tends to predict the polarity of relapse into a subsequent episode in a ratio of about 2:1 to 3:1 and influences response to treatment (Calabrese et al., 2004). Thus, a limitation of Polarity Index is due to the fact that most maintenance trials, from which Polarity Index was calculated, with few exceptions, enrolled enriched populations of patients who were currently or recently manic or mixed. Missing from most study designs was the recruitment of patients with index depressive episodes. Exclusion of depressed patients at enrollment may affect the polarity of mood episodes during the blinded relapse prevention phase since the study design was primarily configured to demonstrate efficacy in the delay or prevention of manic recurrence. The absence of depressive index episodes in a compound whose primary spectrum of efficacy is in depression, biases outcome against the drug, or vice versa; which reflects in Polarity Index calculation as well. However, the main reason why some compounds have only been studied in the context of index mania is their failure to separate from placebo in acute bipolar

depression trials; hence, the bias against index depression is actually caused by the high Polarity Index of the drug, which makes it more suitable for the treatment of mania and the prevention of subsequent manic episodes, and for this reason we believe that the Polarity Index is still fully valid and informative. Hence, Polarity Index should be seen as a concept in continuous evolution, apace with the ongoing research. Although all the available studies published up to date were included, future studies might influence Polarity Index values, especially for agents assessed in a small number of RCTs.

Regarding the Polarity Index of psychological interventions the main limitation (and strength!) of the Polarity Index is, once again, the fact that it derives from RCT data, meaning that issues related to trial design may influence Polarity Index calculations. Among these, issues such as a lack of definition of "placebo comparator" for psychological interventions and uneven number or sessions (or even comparison of an adjunctive intervention to "Treatment As Usual" as control comparator), not only between different interventions, but also among the experimental and control intervention in the same study are evident. The medicaments that patients were assuming differ, and were often

not specified. Study samples were extremely heterogeneous; several trials included patients with Bipolar I or both Bipolar I and II diagnosis, euthymic or acute patients. Even the definition of “euthymia” (syndromic or symptomic) was not uniform, as well as the required duration of euthymia. Differences in exclusion criteria, such as the number of previous episodes and presence of comorbid pathologies are also common between studies. Furthermore the used scales and outcome measures are highly heterogeneous. Above all, the name of intervention (e.g. cognitive behavioural therapy) does not necessarily mean that same treatment protocol was applied; reason why, unlike the Polarity Index for drugs, we were unable to pool data when more studies were available for one intervention.

The Polarity Index (of both drugs and psychological interventions) does not say anything about the absolute efficacy of the intervention, but about the efficacy profile (the higher the number, the more biased toward preventing mania as opposed to preventing depression). It is a ratio, which does not provide information on NNT of an intervention, but rather tells us how balanced an intervention is. Both of these concepts, NNT and the Polarity Index, need to be considered separately, NNT to

determine the efficacy of an intervention, and Polarity Index to depict its profile.

The main limitations of the naturalistic study that was conducted include the tertiary-centre nature of the Barcelona Bipolar Program at Hospital Clinic, which includes a high percentage of difficult-to-treat patients, as well as the abovementioned issues regarding Polarity Index metric. Id est, Polarity Index could not be calculated for all drugs used in treatment of Bipolar Disorder since long-term trials were not conduced for all the agents. In some cases, as for Valproate and Oxcarbazepine, Polarity Index may not be reliable due to the failure to separate from placebo during the pivotal maintenance treatment studies, thus we have excluded them from the analysis. Polarity Index was retrieved from results of clinical trials, thus issues related to trial design itself (adjunctive versus monotherapy design, enrollment of enriched populations of patients who were mainly currently or recently manic or mixed) may have biased the results as previously discussed. An interesting issue is that most maintenance trials assessed samples enriched for efficacy; however, lamotrigine trials were unique in sense that they included study sample enriched for tolerability, and not efficacy,

which may have accounted for to the high NNT detected for lamotrigine (50.4 for mania prevention and 20.2 for prevention of depression) (Popovic et al., 2011; Bowden et al., 2003; Calabrese et al., 2003). Furthermore, one has to bear in mind that the calculation of the mean Polarity Index could not reflect the pharmacokinetic and pharmacodynamic interactions of drugs in combination therapy.

7. CONCLUSIONS

The review of clinical effectiveness of drugs and psychological interventions by the means of NNT comparison aimed to investigate all the treatments approved as maintenance therapy in bipolar disorder. Most of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for the prevention of manic and/or depressive relapses. The comparison of NNT values of the available medicaments may represent a useful adjuvant in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with bipolar disorder.

Overall, our findings indicate that anticonvulsants, and particularly lamotrigine, appear more effective for prevention of depressive episodes, while atypical antipsychotics and lithium may have a preponderant mania recurrence-preventing action.

The Polarity Index may be influenced by the capacity of a given drug to reduce dopamine outflow in the brain, in the sense that the stronger the antidopaminergic action, the higher the Polarity Index and the greater the bias toward preventing mania rather than depression.

Since single drugs have shown differences in efficacy for the prevention of one pole over the other, different drugs should be prescribed according to the predominance of manic or depressive episodes. Since a patient with a predominant depressive polarity is much more likely to relapse into a depressive episode, and therefore a suitable prophylaxis for that patient might be an agent that has been shown to have significant efficacy in preventing relapse of depressive episodes, such as lamotrigine. Similarly, a patient who has predominant manic polarity might require a stronger antimanic prophylactic agent, such as an atypical antipsychotic or lithium, in order to prevent further relapse of manic episodes.

When combining drugs, it may be advisable to combine those which have different Polarity Index in order to have "complementary" efficacy profile, especially in patients who do not present a predominant polarity.

Polarity Index may guide treatment choice in the context of personalized patient care, not only for pharmacological treatments but also, and maybe even more so, given the lack of any similar tools, for adjunctive psychotherapeutic interventions. The fact that the Polarity Index of most pharmacotherapies and

psychotherapies may be complementary would encourage combinations of the two. This metric may help, in the absence of a sufficient number of comparative long-term trials, to understand the relative efficacy profile of adjunctive psychological interventions used in maintenance treatment of bipolar disorder and perhaps design interventions with specific profiles.

Predominant polarity, proposed as a course specifier of particular relevance for long-term therapeutic decision-making process and outcome predictor (Tohen et al., 2009) in DSM-V (Colom and Vieta, 2009), finds its clinical expression in Polarity Index. The present study not only provides further evidence to the importance of considering patients' predominant polarity, but also examines the actual use of the Polarity Index in routine clinical practice.

The results of the present naturalistic study confirm the usefulness of Polarity Index metric in maintenance treatment of bipolar disorder. Important clinical differences between predominantly manic and predominantly depressed patients emerged, and justify the need for differentiated therapeutic approach in the two groups.

Our study shows that the treatment of patients with MPP was oriented mostly towards mania prevention, as evidenced by higher Polarity Index, while treatment of DPP patients was characterized by lower mean Polarity Index, thus directed towards preventing depression. Likewise, the choice of the specific drug, even within the same class, varied in accordance with patients' predominant polarity - Second Generation Antipsychotics with stronger antimanic vs. antidepressant properties were prescribed more often in the Manic Polarity group, and vice versa, mood stabilizers with lower Polarity Index were prescribed more frequently in Depressive Polarity patients. Assuming that specialized care centers may provide higher standards of care and better outcomes than non-specilized settings (Kessing, in press), the Polarity index may be helpful as a tool to assess the quality of maintenance prescription for bipolar patients; hence, if MPP patients receive higher PI regimens than DPP patients, the treatment is likely to be evidence based.

8. FUTURE DIRECTIONS

The results of the study suggest that the use of Polarity Index might lead to an individualized optimization in the treatment of bipolar patients. In order to replicate the findings, further studies applying Polarity Index to the pharmacological and/or psychological treatment of bipolar patients are required. At the moment, Polarity Index metric is being validated in Porto Alegre, Brazil and Thessaloniki, Greece.

A possible evolution of my work consists in correlating antidepressive vs. antimanic dosages of each drug, calculated from all the available clinical trials, with the Polarity Index, in attempt to predict the most effective treatment for each individual patient. This could be one of the first steps in the creation of "precision psychiatry", with an important impact above all on therapeutic management of patients with bipolar disorder, but could also carry a secondary benefit of being able to direct the choice of dosages and focus on specific sub populations of bipolar patients that would be most likely to respond to a certain drug and thus could be of interest also for clinical trials.

Successful long-term management often appears to require combination treatment, and although assessing combined treatments went beyond the aims of our study, lack of such trials, e.g., lamotrigine as add-on treatment, should be an object of future research. Randomized clinical trials for maintenance treatment of Bipolar Disorder are not only scarce; they are completely lacking for various agents. Carbamazepine is a clear example; although it was the first agent after lithium to be advocated for long-term treatment of bipolar disorder and 2 lithium controlled studies indicate drug's efficacy in relapse prevention (Greil et al., 1997; Hartong et al., 2003), by the time the research was conducted there were no available long term placebo-controlled trials and thus Polarity Index of carbamazepine, could not be calculated. Future research needs to address the long-term effectiveness and the Polarity Index of agents such as carbamazepine, oxcarbazepine, valproate and newer antipsychotics such as paliperidone or asenapine.

As to the psychological interventions, future studies are needed in order to isolate the “active ingredients” responsible for therapeutic response and thus enable to design new, eventually

shorter, interventions that would focus on the essential components in order to prevent episodes of different polarity.

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10.) TABLES AND FIGURES

Table 1. Characteristics of randomized controlled trials included in NNT analyses for Recurrence Prevention of Pharmacological Agents used for Maintenance Treatment of Bipolar Disorder

Trial	Inclusion criteria (maintenance phase)	Duration (weeks)	Number randomized	Dosage (mg/day) or plasma levels / Mean dosage
Bowden et al., 2000	Bipolar I 18-70 years Manic episode ≤3 months before randomization. MRS ≤11 DSS ≤13 GAS > 60, No serious suicidal risk	52	VPA: 187 LI: 90 PLA:92	VPA: 71-125 µg/mL LI: 0.8-1.2 mmol/L
Bowden et al., 2003	Bipolar I ≥ 18 years Current or recent (hypo)mania ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	76	LAM: 59 LI: 46 PLA:70	LAM: 100-400mg/die LI: 0.8-1.1 mEq/L
Bowden et al., 2010	Bipolar I ≥ 18 years Curent or recent manic/ mixed episode MRS≥14	24	ZIP+LI/VPA= 127 PLA+LI/VPA= 113	ZIP: 80-160 mg/die LI: 0.6–1.2 mEq/L Mean: 0.7-0.9 mEq/L VPA:50-125 µg/mL Mean: 67.4-72.8
Calabrese	Bipolar I and II	26	LAM: 90	LAM: 100–300

et al., 2000	Rapid cycling ≥ 18 years ≤14 HAM-D ≤12 MRS < 3 on item 3 HAM-D stable for 4 weeks		PLA: 87	mg/day
Calabrese et al., 2003	Bipolar I ≥ 18 years Current or recent MDE ≥1 additional (hypo)manic and 1 depressive episode in the past 3 years	72	LAM: 221 LI: 121 PLA:121	LAM:50-400mg/die Mean:200mg/die LI: 0.8-1.1 mEq/L Mean: 0.8±0.3 mEq/L
Keck et al., 2007	Bipolar I ≥ 18 years YMRS≤ 10 MADRS≤ 13 No hospitalization in previous 3 months	100	ARI=78 PLA=83	ARI: 15-30mg/day Mean: 23.8 mg/day
Macfadden et al., 2009	Bipolar I 18-70 years ≥4 episodes in the past year	52	RLAI+ TAU= 65 PLA+ TAU= 59	RLAT: 25-50mg / 2 weeks
Prien et al., 1973	Manic-depressive, manic type	24*	LI:101 PLA: 104	LI: 0.5-1.4 mEq/L
Quiroz et al., 2010	Bipolar I 18-65 years Recent manic/mixed episode or stable patients with ≥1 mood episode in past 4 months	96	RLAI=140 PLA= 136	RIS: 12.5-50 mg i.m. Mean:25mg
Suppes et al., 2009	Bipolar I ≥ 18 years YMRS≤ 10 MADRS≤ 13	104	QUE+LI/VPA= 310 PLA+LI/VPA= 313	QUE: 400–800mg/day Mean: 519 mg/die

				LI: 0.5–1.2 mEq/L Mean: 0.71-0.74 mEq/L VPA:50-125 µg/mL Mean: 68.91-71.38 µg/mL
Tohen et al., 2006	Bipolar I ≥ 18 years YMRS≤ 12 HAM-D≤ 8 2 prior mixed or manic episodes in past 6 years	48	OLZ=225 PLA= 136	OLZ: 5–20 mg/day
Tohen et al., 2004	Bipolar I 18-70 years YMRS≤ 12 HRSD-21≤ 8	72	LI/VPA+PLA= 48 LI/VPA+OLZ= 51	OLZ:5-20 mg/day Mean: 12.5 mg/day LI: 0.66-0.86 mEq/l VPA: 60.1-73.8 µg/mL
Vieta et al., 2008(b)	Bipolar I or II ≥ 18 years YMRS≤ 12 MADRS≤20 No acute phases in 6 months	52	OXC+LI=26 PLA+LI=29	OXC: 1200 mg/day LI:0.6 mEq/l
Vieta et al., 2008 (a)	Bipolar I ≥ 18 years YMRS≤ 12 HAM-D≤ 12	104	QUE+LI/VPA= 336 PLA+LI/VPA= 367	QUE: 400 -800 mg/day Mean: 497 mg/day LI: 0.5–1.2 mEq/L VPA:50-125 µg/mL

Weisler et al., 2008	Bipolar I YMRS ≤12 MADRS ≤12 Acute current or recent (past 26 weeks) manic, depressive, or mixed index episode treated with QUE	104	QUE= 404 LI= 364 PLA= 404	QUE: 300-800 mg/day Li: 0.6-1.2 mEq/L

∗ NNT analyses refer to 12 month- period. Trials are in alphabetic order. PLA=placebo, ARI= aripiprazole, OLZ= olanzapine, LI=lithium, VPA= valproate, QUE=quetiapine, RLAI= risperidone long acting injection, TAU= treatment as usual, ZIP=ziprasidone, LAM=lamotrigine, OXC= oxcarbazepine

Table 2. Relapse rates reported in Randomized Controlled Trials of Pharmacological Agents used for Maintenance Treatment of Bipolar Disorder

	Any episode n (%)		**Mania n (%)**		**Depression n (%)**	
	PCB relapse	**Drug relapse**	**PCB relapse**	**Drug relapse**	**Placebo relapse**	**Drug relapse**
Aripiprazole (Keck et al., 2007)	43/83 (51.81)	25/77 (32.47)	23/83 (27.71)	9/77 (11.69)	13/83 (15 .66)	11/77 (14.28)
Olanzapine (Tohen et al., 2006)	109/136 (80.14)	105/225 (46.66)	44/136 (32.35)	27/225 (12)	53/136 (38.97)	68/225 (30.22)
Olanzapine + LI/VPA (Tohen et al., 2004)*	21/38 (55.26)	11/30 (36.66)	11/38 (28.94)	6/30 (20)	15/38 (39.47)	7/30 (23.33)
Quetiapine + LI/VPA (Vieta et al., 2008)	180/367 (49.04)	62/336 (18.53)	96/367 (26.16)	36/336 (10.71)	84/367 (22.89)	26/336 (7.74)
Quetiapine + LI/VPA (Suppes et al., 2009)	163/313 (52.08)	63/310 (20.32)	61/313 (19.49)	22/310 (19.49)	102/313 (32.59)	41/310 (13.23)
Quetiapine (Weisler, 2009)	343/404 (84.90)	162/404 (40.10)	291/404 (72.03)	121/404 (29.95)	186/404 (46.04)	65/404 (16.09)
Risperidone LAI (Quiroz et al., 2010)	76/135 (56.29)	42/140 (30)	62/135 (45.93)	22/140 (15.71)	41/135 (10.37)	14/135 (14.29)
Risperidone LAI +TAU (Macfadden et al., 2009)	27/59 (45.76)	15/65 (23.08)	12/59 (20.34)	5/65 (7.69)	11/59 (18.64)	8/65 (12.31)
Ziprasidone + LI/VPA (Bowden et al., 2010)	36/111 (32.43)	25/127 (19.69)	14/111 (12.61)	7/127 (5.51)	16/111 (14.41)	16/127 (12.60)
Lamotrigine (Bowden et al., 2003)	49/70 (70)	28/59 (47.46)	22/70 (31.43)	16/59 (27.12)	21/70 (30)	8/59 (13.56)
Lamotrigine (Calabrese et al.,2003)	66/119 (55.46)	115/215 (53.49)	19/119 (15.97)	38/215 (17.67)	47/119 (39.50)	77/215 (35.81)

Lamotrigine (Calabrese et al., 2000)	64/87 (73.56)	53/90 (58.89)	N.A.	N.A.	N.A.	N.A.
Lamotrigine (Goodwin et al., 2004)	115/191 (60.21)	143/280 (51.07)	47/191 (24.61)	58/280 (20.71)	68/191 (35.60)	85/280 (30.36)
Lithium (Prien et al., 1973)	71/104 (68.27)	36/101 (35.64)	53/104 (50.96)	23/101 (22.77)	14/104 (13.46)	9/101 (8.91)
Lithium (Goodwin et al., 2004)	115/191 (60.21)	74/167 (44.31)	47/191 (24.61)	18/167 (10.78)	68/191 (35.60)	56/167 (33.53)
Lithium (Bowden et al.,2003)	49/70 (70)	18/46 (39.13)	22/70 (31.43)	6/46 (13.04)	21/70 (30)	10/46 (21.74)
Lithium (Calabrese et al., 2003)	66/119 (55.16)	56/120 (46.67)	19/119 (15.97)	10/120 (8.93)	47/119 (33.50)	46/120 (38.33)
Lithium (Bowden et al., 2000)	36/94 (38.30)	28/91 (30.77)	21/94 (22.34)	19/91 (20.80)	15/94 (9.89)	9/91 (15.96)
Lithium (Weisler et al., 2009)	343/404 (84.90)	149/364 (40.93)	291/404 (72.03)	102/364 (28.02)	186/404 (46.04)	66/364 (18.13)
Valproate (Bowden et al., 2000)	36/94 (38.29)	45/187 (24.06)	21/94 (22.34)	33/187 (17.65)	15/94 (15.96)	12/187 (6.42)
Oxcarbazepine +LI (Vieta et al., 2008)	17/29 (58.62)	10/26 (38.46)	8/29 (27.58)	4/26 (15.38)	9/29 (31.03)	3/26 (11.54)

TAU= Treatment as usual; LI=Lithium; VPA=Valproate

Table 3. Number needed to treat (NNT) values for Recurrence Prevention of Pharmacological Agents used for Maintenance Treatment of Bipolar Disorder

	NNT **Any episode** 95% CI	**NNT** **Mania** 95% CI	**NNT** **Depression** 95% CI
Aripiprazole (Keck et al., 2007)	**6** [2.9-23]	**7** [3.6, 24.9]	50.0 [7.7, Infinity]
Olanzapine (Tohen et al., 2006)	**3** [2.3, 4.2]	**5** [3.4, 8.8]	12 [5.3, Infinity]
Olanzapine + Lithium/Divalproex (Tohen et al., 2004)*	6 [2.4, Infinity]	12 [3.4, Infinity]	6 [2.6, Infinity]
Quetiapine + Lithium/Divalproex (Vieta et al., 2008)	**4** [2.7-4.2]	**7** [4.8,10.1]	**7** [4.9, 10.0]
Quetiapine + Lithium/Divalproex (Suppes et al., 2009)	**4** [2.6, 4.1]	**9** [5.7, 14.0]	**6** [3.9, 7.7]
Quetiapine (Weisler et al., 2009)	**3** [2, 2.6]	**3** [2, 2.8]	**4** [2.8, 4.2]
Risperidone LAI (Quiroz et al., 2010)	**4** [2.4, 5.6]	**4** [2.5, 5.0]	26 [8.6, Infinity]
Risperidone LAI + Treatment as Usual (Macfadden et al., 2009)	**5** [2.6, 15.7]	**8** [4.0, 198.7]	16 [5.2, Infinity]
Ziprasidone + Lithium/Divalproex (Bowden et al., 2010)	**8** [4.2, 61.5]	15 [6.9,Infinity]	56 [9.5, Infinity]
Lamotrigine	**5**	24	**7**

(Bowden et al., 2003)	[2.6, 17.0]	[5.0, Infinity]	[3.3, 38.5]
Lamotrigine (Calabrese et al.,2003)	51 [7.6, Infinity]	59 [10.0, Infinity]	28 [6.9, Infinity]
Lamotrigine (Calabrese et al.,2000)	**7** [3.5, 108.8]	N.A	N.A.
Lamotrigine (Goodwin et al., 2004)	11 [5.5, 1764.7]	26 [8.6, Infinity]	20 [7.2, Infinity]
Lithium (Prien et al., 1973)	**4** [2.2, 5.1]	**4** [2.5, 6.4]	22 [7.6, Infinity]
Lithium (Goodwin et al., 2004)	**7** [3.8, 17.7]	**8** [4.6, 16.3]	49 [8.4, Infinity]
Lithium (Bowden et al.,2003)	**4** [2.3, 20.5]	**6** [3, 26.4]	13 [4.1, Infinity]
Lithium (Calabrese et al., 2003)	12 [4.7, Infinity]	14 [6.3, Infinity]	86 [7.4, Infinity]
Lithium (Bowden et al., 2000)	14 [4.7, Infinity]	69 [7.5, Infinity]	17 [6.4, Infinity]
Lithium (Weisler et al., 2009)	**3** [2, 2.6	**3** [2.2, 2.7]	**4** [2.8, 4.4]
Valproate (Bowden et al., 2000)	**7** [3.9, 37.7]	22 [6.8, Infinity]	11 [5.6, 74.3]
Oxcarbazepine + Lithium (Vieta et al., 2008)	5 [2.2, Infinity]	9 [3.0, Infinity]	6 [2.5, Infinity]

* Data referring to symptomatic relapse. CI= Confidence Interval, LAI= Long Acting Injection. Note: Significant NNTs are in bold letters

Table 4. Characteristics and relapse rates of the included trials for adjunctive Psychotherapies in Maintenance treatment of Bipolar Disorder

Trial characteristics				**Study Results**			
Intervention	**Control**	**Inclusion criteria (maintenance phase)**	**Trial Characteri-stics**	**Manic Relapse**		**Depressive Relapse**	
				Control Group	Exper. Group	Control Group	Exper. Group
BTDI (Perry et al., 1999)	Routine care	BD I or II ≥2 relapses, 1 in the previous year Age: 18-75 No primary substance abuse	7-12 sessions	11/35 31.43%	2/33 6%	9/35 25.71%	11/33 33.33%
CGPE (Reinares et al., 2008)	Meetings without intervention	Caregivers of BD I or II patients, Age: 18-60 euthymia ≥3 months, on pharmacological treatment for BD	12 weeks of intervention and 1 year follow-up	21/56 37.5%	10/57 17.54%	23/56 41.07%	17/57 29.82%
CBT (Lam et al., 2003)	TAU	BD I Pharmacological treatment Age: 18-70 years ≥2 episodes in past 2 years or 3 episodes in past 5 years Current euthymia; BDI<30, MRS<9 No substance use disorders, not suicidal	14 sessions in first 6 months + 2 booster sessions in second 6 months, performed by psychologists	16/48 33.33%	21/48 43.75%	10/48 20.83%	25/48 52.08%
CBT (Lam, 2005)	TAU	BD I ≥2 episodes in past 2 years/ 3	30 months CBT+ medication vs.	31/46 67%	23/46 50%	17/44 38%	32/48 66%

		episodes in 5 years prior to recruitment. Not actively suicidal, no substance use disorder	medication only 12–18 individual sessions in 6 months				
CBT (Meyer and Hautzinger, 2011)	Supportive treatment	BD I or II Age: 18-65 Assuming medication No: primary diagnosis of non-affective disorder, current affective episode, substance-induced affective disorder or affective disorder due to a general medical condition, no current substance dependency, no cognitive impairment, no current psychological treatment.	20 sessions of CBT or Supportive Therapy over 9 months. Follow up: 24 months.	8/38 21.05%	10/38 26.32%	14/38 36.84%	7/38 18.42%
CBT (Scott et al., 2006)	TAU	BD I or II Age ≥18 years ≥2 acute episodes,1in previous year; contact with mental health services No: rapid-cycling, BD secondary to an organic cause, severe borderline	72 weeks 20 weekly sessions of CBT until week 15 and then with gradually reducing frequency until week 26 + 2 'booster sessions'	25/126 19%	28/127 22%	39/126 30%	39/127 30%

		PD, suicidal ideation/ intent in past 3 months continuous substance misuse, current mania, current systematic psychological treatment					
ERP (Lobban et al., 2010)	TAU	BD I or II ≥2 relapses, 1 in the past 12 months or 2 in past 3 years Euthymic ≥4wks No rapid cycling, primary substance abuse or organic cause	6 x 1h sessions Care coordinators (trained by a nurse)	8/40 20%	9/40 22.5%	16/40 40%	17/40 42.5%
FFT (Miklowitz, 2003)	Crisis management-nt intervention and TAU	BD I or II. Acute episode in the past 3 months Aged 18-65 years No developmental disability or neurologic disorder No substance use disorders in the previous 6 months Regular contact with a caregiver English speaking	2 years Prior episodes 7.9±17.9 (FFT) 5.7±13.4 (CM) FFT: 21 sessions CM: 2 sessions Duration: 9 months. Pharmacotherapy for 2 study years.	6/70 8%	5/31 16%	26/70 37%	6/31 19%
PE	Meetings	BD I or II	20 x 90-	20/60	12/60	19/60	8/60

(Colom et al., 2003)	without interventi on	Age: 18-65 years 6 months of euthymia (YMRS <6; HDRS-17 <8) No substance abuse, no mental retardation or organic brain damage, no deafness	minute sessions + 2yrs follow up	33.33%	20%	31.67%	13.33%
PE (Colom et al., 2009)	Meetings without interventi on	Note: 5-year follow up of the Sample in Colom et al.,2003 BD I or II Age: 18-65 years 6 months of euthymia (YMRS <6; HDRS-17 <8) No substance abuse, no mental retardation or organic brain damage, no deafness	20x90-minute sessions + 2yrs follow up	48/60 80%	32/60 53.33%	50/60 83.33%	29/60 48.33%

BD= Bipolar Disorder; BTDI= Brief Technique-Driven Intervention; PE= Psychoeducation; CGPE=Caregiver Group Psychoeducation; CBT= Cognitive Behavioural Therapy; TAU= Treatment as usual; ERP= Enhanced Relapse Prevention; FFT= Family Focused Therapy

Table 5. Excluded trials and reasons for their exclusion

Trial	Reason for exclusion
Ball, 2006	Depression and mania relapse rates not reported
Castle, 2010	Depression and mania relapse rates not reported
Clarkin, 1998	Depression and mania relapse rates not reported
Cochran, 1984	Relapse rate not assessed ; Small sample size
D'Souza	Depression and mania relapse rates not reported
Frank, 2005	Relapse rates not reported
Gomes 2011	Depression and mania relapse rates not reported
González-Isasi 2010	Small sample size
Johnson, 2009	Small sample size; Absence of a control group
Kessing 2011	Sample composed of bipolar and depressed patients; Relapse rates not published
Miklowitz 2008	Adolescents Depression and mania relapse rates not reported
Miklowitz, 2007	Depression and mania relapse rates not reported
Miller 2008	Depression and mania relapse rates not reported
Miller, 2004	Assessed only time to recovery, not recurrence of mood episodes
Perlick 2010	Depression and mania relapse rates not reported
Rea 2003	Absence of a control group
Simon 2006	Relapse rates not clearly reported
Solomon 2008	Small sample size
Van Gent, 1991	Small sample size
Weiss 2000,2007,2009	Depression and mania relapse rates not reported
Williams 2008	Depression and mania relapse rates not reported
Zaretsky 2008	Absence of a control group, Depression and mania relapse rates not reported

Table 6 . NNT for prevention of mania, depression, and any mood episode and Polarity Index of each study.

	NNT Mania	**NNT Depression**	**NNT Any episode**	**Polarity Index**
Brief technique-driven interventions (Perry et al., 1999)	3.9	13.1	11.3	3.36
Enhanced relapse prevention for BD (Lobban et al., 2010)	40	40	20	1
Cognitive behavioural therapy (Lam et al., 2003)	9.6	3.2	4.8	0.33
Psychoeducation (Colom et al., 2003)	7.5	5.5	4.6	0.73
Caregiver group psychoeducation (Reinares et al., 2008)	5.0	8.9	4.2	1.78
Family-focused therapy (Miklowitz et al., 2003)	13.2	5.6	5.3	0.42
Cognitive behavioural therapy (Lam et al., 2005)	5.7	3.6	4.9	0.63
Cognitive behavioural therapy (Meyer and Hautzinger, 2011)	19	5.4	4.8	0.89
Psychoeducation (Colom et al., 2009)	7.5	3.7	2.9	0.78

NNT= Number Needed to Treat, BD= Bipolar Disorder

Table 7. Demographic and clinical characteristics of the study sample

	Manic Polarity n (%)	**Depressive Polarity n (%)**	**χ^2**	**p**
Gender			11.591	0.001*
Male	69/114 (60.53)	56/143 (39.16)		
Level of working activity			1.844	0.175
Good	74/110 (67.27)	77/131 (58.78)		
Authonomy			2.179	0.140
Good	95/109 (87.16)	104/130(80.00)		
Educationallevel			0.601	0.438
Qualified	50/111 (45.05)	68/136 (50.00)		
Subtype			23.530	0.000*
BD I	100/113(88.50)	86/140 (61.43)		
BD II	13/113(11.50)	54/140 (38.57)		
First episode			76.365	0.000*
Depression	39/110(35.45)	119/134 (88.81)		
Primary Substance use			17.174	0.001*
Yes	68/102 (66.67)	61/128 (47.65)		
Primary Life events			6.915	0.009*
Yes	49/92 (53.26)	85/120 (70.83)		
Substance use			27.853	0.366
None	27/108 (25)	48/136 (35.29)		
Alcohol	31/108 (28.70)	36/136 (26.48)		
Cannabinoids	29/108 (26.85)	53/136 (38.97)		
Rapidcycling			0.000	0.992
Yes	12/106(11.32)	15/132(11.36)		
Melancholia			11.281	0.001*
Yes	23/100 (23.0)	54/121 (44.63)		

Catatonia Yes	4/99 (4.04)	5/121 (4.13)	0.001	0.973
Seasonal pattern Yes	21/102(20.59)	38/130 (29.23)	2.251	0.134
Psychotic symptoms Yes	75/109(68.81)	66/132(50.0)	8.699	0.003*
Psychosis at I episode Yes	55/90 (61.11)	35/90 (38.88)	14.915	0.000*
Suicidal Ideation Yes	52/92 (56.52)	85/127 (66.93)	2.467	0.116
Suicide Attempts Yes	22/100 (22.0)	43/124 (34.68)	4.319	0.038*
Family History of Affective Disorders Yes	64/106(60.38)	85/128 (66.41)	0.911	0.340
Family History of Suicide Yes	12/107(11.21)	22/126 (17.46)	1.811	0.178
Family History of Psychiatric Disorders Yes	86/108(79.62)	103/132 (78.03)	0.091	0.763
Atypical depression Yes	13/94 (13.83)	26/116 (22.41)	2.530	0.112
Medical Comorbidity Yes	18/41 (43.90)	21/59 (35.59)	0.702	0.402
Psychoeducation Yes	17/103(16.50)	14/127 (11.02)	3.229	0.199
Compliance Good	71/105(67.62)	82/126 (65.08)	0.165	0.684
Axis I comorbidity Yes	27/105(25.71)	37/131 (28.24)	20.877	0.589
Axis II comorbidity			20.647	0.192

Yes	18/105(17.14)	32/132 (24.24)		
Axis III comorbidity Yes	45/97 (46.39)	49/114 (42.98)	3.543	0.315

Table 8. Differential Quantitative Features between Manic Polarity and Depressive Polarity Groups

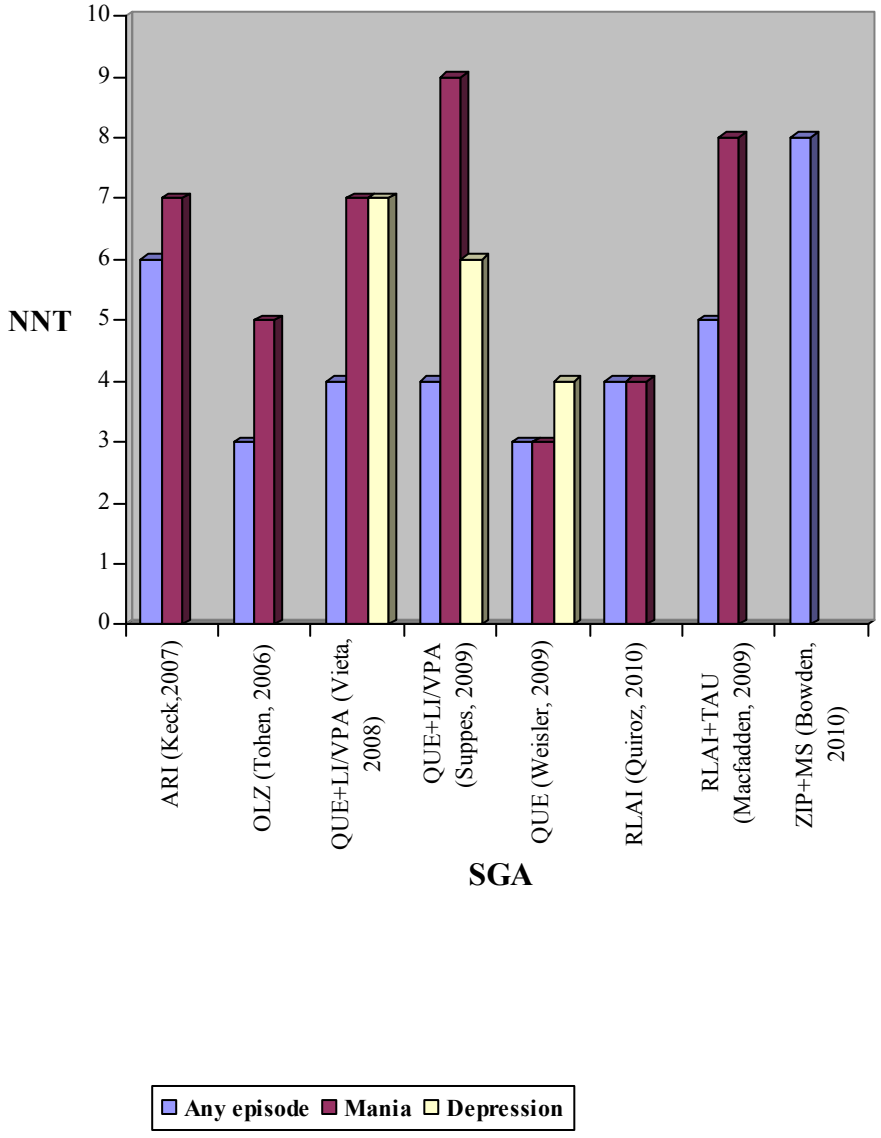
	Manic Polarity (n=114) **Mean (SD)**	**Depressive Polarity** (n= 143) **Mean (SD)**	***t/ U***	***p***
Age	47.29(14.50)	57.00(27.85)	-3.375	0.001*
Age of onset	26.16 (10.70)	30.57(11.82)	-3.009	0.003*
Age of firsthospitalization	29.89 (13.56)	37.35(14.185)	-3.268	0.001*
Number of hospitalizations	2.17 (2.566)	1.40 (1.78)	2.648	0.009*
Total number of episodes	11.67(18.23)	12.21 (16.40)	-0.245	0.807
Number of manicepisodes	3.79 (4.65)	0.98 (1.33)	6.202	0.000*
Number of hypomanic episodes	4.79 (9.94)	2.35 (4.50)	2.336	0.021*
Number of depressive episodes	2.86 (5.86)	8.20 (11.66)	-4.755	0.000*
Number of mixed episodes	0.45 (1.54)	0.73 (1.61)	-1.360	0.175
Number of suicide attempts	0.80 (3.841)	0.75 (1.366)	109.908	0.129

Table 9. Polarity Index of drugs in Manic and Depressive Polarity groups

	Manic Polarity (n=114)		**Depressive Polarity** (n= 143)						
	Mean	SD	Mean	SD	p	Mann-Whitney U	p	Kolmogorov-Smirnov Z	p
Polarity Index AP+MS	3.68	3.19	2.22	2.36	0.001*	3385.5	0,000*	2.069	0.000*
Polarity Index AP	6.78	4.68	4.77	4.53	0.044*	1281.5	0.006*	1.425	0.035*
Polarity Index MS	1.31	0.23	1.14	0.38	0.001*	2679.0	0.001*	1.429	0.034*

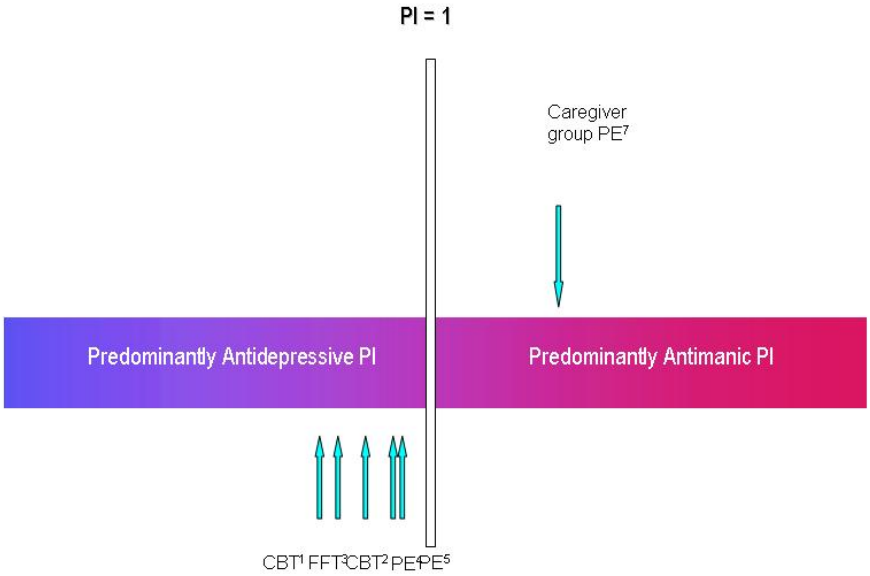
AP= Antipsychotics, MS= Mood Stabilizers; SD= Standard Deviation

Figure 1. Second Generation Antipsychotics in Maintenance Treatment of Bipolar Disorder (significant NNTs)



SGA= second generation antipsychotic, MS= mood stabilizer, PLA=placebo, ARI= aripiprazole, OLZ= olanzapine, LI=lithium, VPA= valproate, QUE=quetiapine, RLAI= risperidone long acting injection, TAU= treatment as usual, ZIP=ziprasidone

Figure 2. Logarithmic distribution of Polarity Index for the assessed interventions



PI= Polarity Index, CBT= cognitive behavioural therapy, FFT= family-focused therapy, PE= psychoeducation [1]Lam et al., 2003; [2]Lam et al., 2005; [3]Miklowitz 2003; , 2011; [4]Colom et al.,2003; [5]Colom et al., 2009;; [7]Reinares 2008