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Review article

Bipolar spectrum disorder: What evidence for pharmacological treatment? A systematic review

Vincent Hede[a], Sophie Favre[a], Jean-Michel Aubry[a,b], Hélène Richard-Lepouriel[a,*]

[a] Mood disorder unit, Psychiatric specialties service, Geneva University Hospital, Rue de Lausanne 20, CH-1201 Geneva, Switzerland
[b] Department of Psychiatry, University of Geneva, Geneva, Switzerland

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ABSTRACT

Background and Objectives: Bipolar spectrum disorder (BSD) is an extended concept of bipolar disorder (BD) that includes conditions that do not fulfill the criteria. There is no recommendation today about its treatment. We reviewed relevant literature focusing on pharmacological treatments, looking for high-strength evidence leading to guidelines.

Methodology: A literature search was conducted using MedLine / PubMed database and Google Scholar up to September 2018. Search words were related to BSD and pharmacological treatment.

Results: The literature search yielded 621 articles. Out of these, 35 articles met our selection criteria. There was limited high quality data. Only one randomized control trial (RCT) and one randomized open label trial were found. Most studies used different definition of BSD.

Conclusions: There is a considerable lack of data and no evidence supporting efficacy of pharmacological treatment for BSD. There is a need for a consensus on the definition of BSD and more evidence studies to evaluate drug's effectiveness in this condition.

1. Introduction

1.1. Definitions

Recent studies have extended the concept of bipolar disorder (BD) to include a diagnosis of bipolar spectrum disorder (BSD). However, this condition is not precisely defined and remains unclear and heterogeneous. Akiskal (1987) was the first to describe a soft bipolar spectrum that included hyperthymic, cyclothymic, bipolar II, bipolar III and subaffective disorders. The extension of the spectrum, included bipolar I (mania), bipolar I½ (major depressive episode (MDE) and protracted hypomania), bipolar II (MDE and hypomania), bipolar II ½ (MDE and cyclothymic disorder), bipolar III (antidepressant-associated hypomania), bipolar III ½ ('bipolarity masked and unmasked by stimulant abuse'), and bipolar IV (MDE and hyperthymic temperament) (Akiskal and Pinto, 1999). Ghaemi et al. (2001, 2002) proposed a heuristic definition of BSD, with greater weight on family history and antidepressant-induced manic symptoms (Table 1).

In 2002, Angst et al. included in the definition of BSD: Bipolar I disorder; Bipolar II disorder; minor bipolar disorder (dysthymia, minor depression or recurrent brief depression associated with (a) the hypomanic syndrome or (b) hypomanic symptoms only) and pure hypomania (Angst et al., 2003). A more inclusive definition modifying Ghaemi's was put forward by Muzina (2007) with an emphasis on recurrence and impact of mood episodes. In the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013), the diagnostic category of other specified bipolar and related disorder allowed the categorization of patients who presented symptoms that did not meet the full criteria for BP and related disorders, with no mention of BSD (Kaltenboeck et al., 2016).

1.2. Prevalence of BSD

It is difficult to assess the prevalence and/or incidence of BSD because of the lack of a clear definition. One study suggested that BSD might affect up to 6% of the general population (Judd and Akiskal, 2003), while another author reported that 24% of a 20-year prospective community cohort developed some degree of BSD (Angst et al., 2003). A survey in a large clinical sample using broad criteria for the spectrum identified bipolarity in 40% of all outpatients (Akiskal et al., 2006). More recently, other authors reported that the

* Corresponding author.
E-mail addresses: vincent.hede@hcuge.ch (V. Hede), sophie.favre@hcuge.ch (S. Favre), jean-michel.aubry@hcuge.ch (J.-M. Aubry), helene.richard-lepouriel@hcuge.ch (H. Richard-Lepouriel).

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Table 1
Ghaemi's criteria (2002).

A. At least one major depressive episode.
B. No spontaneous hypomanic or manic episodes.
C. Either of the following, plus at least two items from criterion D, or both of the following plus one item from criterion D; C:
  1. A family history of bipolar disorder in a first degree relative,
  2. Antidepressant-induced mania or hypomania.
D. If no items from criterion C are present, six of the following nine criteria are needed:
  1. Hyperthymic personality,
  2. Recurrent major depressive episodes (>3),
  3. Brief major depressive episodes (on average, <3 months),
  4. Atypical depressive symptoms (DSM-IV criteria),
  5. Psychotic major depressive episodes,
  6. Eearly age of onset of major depressive episode (< age 25),
  7. Postpartum depression,
  8. Antidepressant "wear-off" (acute but not prophylactic response),
  9. Lack of response to three antidepressant treatment trials.

aggregate lifetime prevalence of BP-I is 0.6%, of BP-II is 0.4% and of BSD is 3.8% (including subthreshold bipolar disorder) (Merikangas et al., 2007, 2011). In another study with primary care patients, 9.8% were identified with the Mood Disorder Questionnaire – MDQ (Hirschfeld et al., 2000) and received a positive screening for lifetime BD (Das et al., 2005). The incidence of BSD in a community sample was of 9.3% (Zimmerman et al., 2009). Among patients with mood depressive disorder (MDD), 28–41% of this met the criteria for subthreshold bipolar disorder (MDD with subthreshold hypomania) (Perlis et al., 2011; Zimmermann et al., 2009). Another study reported that 47% of people with MDD fulfilled criteria for BD, using the Zurich criteria (no minimum time duration or exclusion criteria were applied) (Angst et al., 2011). The potential bias induced by the sponsorship of a pharmaceutical company was a limitation of this study.

1.3. From diagnosis to pharmacological treatment

The clarification of the diagnosis of BSD is a key issue for the pharmacological treatment. The potential value of broadening the BD diagnosis is still controversial (Mitchell, 2012). There is a risk of over-diagnoses and overuse of medication, linked with subsequent financial ramifications. Patients who may respond to bipolar treatment algorithms can be more clearly identified. There is a possible benefit with a diminution of diagnostic delay in affected people, but it must be balanced against the risk of misuse medications (Strakowski et al., 2011). The number of prescription recommendations for BD in Canada increased by 72.1% from 2002 to 2009, and then dropped by 24.8% from 2009 to 2010, for all classes of medications (Bulloch et al., 2012). The promotion of BSD may have resulted in a substantial increase in treatment (Bulloch et al., 2012). There is a need for solid evidence that treatments that are effective for the classical forms of BD are also effective for spectrum conditions, although recent classifications tend to suggest a more aggressive psychopharmacological approach (Paris, 2014).The aim of this review is to examine the efficacy of pharmacological treatments for BSD.

2. Method

This systematic literature search was conducted through MedLine / PubMed database and Google Scholar up to September 2018 using the PRISMA statement (Moher et al., 2009).

2.1. Inclusion criteria

We included studies published in academic journals that: (a) were either controlled trials (with a control group), uncontrolled pre- and post-intervention studies (without a control group), case-studies or reviews, (b) included people with BSD.

2.2. Information sources and searches

One author (HRL) carried out the article search. The articles were subsequently independently checked by a second author (VH) for applicability. The reference list of included articles and relevant review articles was systematically reviewed for additional studies. Search words used included: "bipolar spectrum", "subthreshold bipolar*", "soft bipolar*", "minor bipolar*", "subsyndromal bipolar*". These search words were combined with the search term "treatment" with the Boolean operator AND. Since subthreshold pediatric BD is very specific and has already been studied in a recent review and meta-analysis (Vaudreuil et al., 2019), we have chosen to consider only adult patients. Thus, BD in childhood was excluded, as well as the following search terms "pediatric", "child*" "offspring", (combined with the Boolean operator NOT.)

2.3. Study selection

A database was created with the potentially relevant studies (from the earliest indexed articles to September 2018). We excluded articles including bipolar disorder (I and II) and cyclothymia. These disorders are clearly defined and are not in the BSD. We excluded studies with non-pharmacological treatments (such as light therapy, psychotherapy…).

2.4. Data extraction

Data extraction was led by two author (HRL and VH). Information was extracted by: (1) study design - randomisation, description of allocation concealment and blinding; (2) study participants – inclusion and exclusion criteria, country, region, population studied, and baseline characteristics such as age, sex, socio-economic indicators and mental health; (3) intervention and comparison groups – medication frequency, intensity, duration, mode of delivery.

2.5. Data synthesis

We could not conduct a quantitative meta-analysis because of the heterogeneity of the studies included. A best-evidence synthesis was used to identify the key results and limitations of each study. The results of controlled and uncontrolled interventions are reported.

3. Results

3.1. Study selection

The search strategy produced initially total of 621 articles. 61 articles were excluded because they were redundant between the two databases. Articles with bipolar disorder (I and II) and cyclothymia without further mention of the BSD were also excluded, as well as articles reporting non-pharmacological treatment (as light therapy, psychotherapy…). After this selection, 118 articles were eligible. Only 35 articles revolved around the question of BSD treatment. The details of this search procedure are summarized in Fig. 1.

Among the 35 studies included, there was one randomized control trial (RCT), one randomized open label trial, three observational studies, four prospective studies, 10 case report or case series, nine expert opinion and seven literature review.

3.2. Details of included trials/studies

All articles included are summarized either in Table 2 or Table 3. Table 2 describes the clinical trials, RCT, pilot studies, observational reports, case series or case reports. Table 3 includes other type of

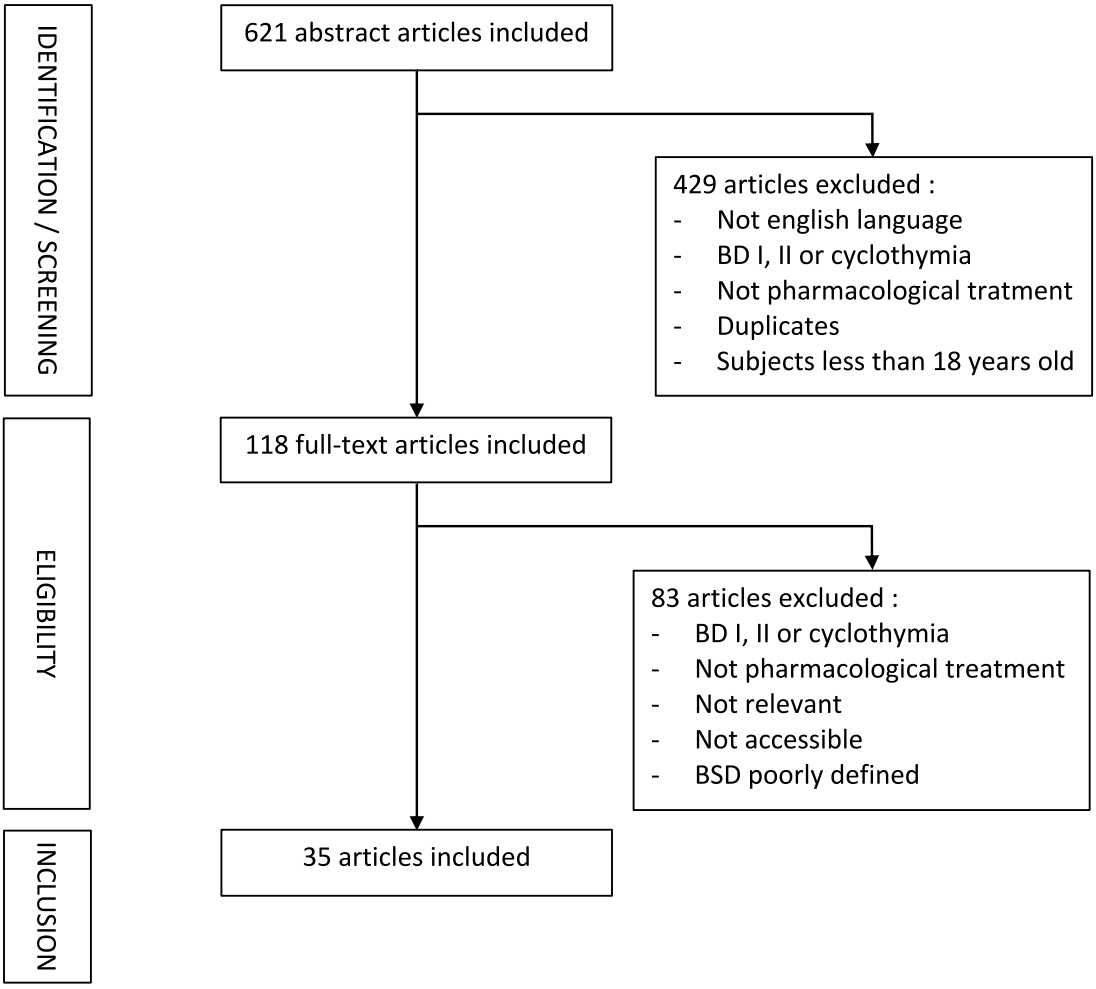

Fig. 1. Flow-shart.

studies such as reviews, overviews, editor letters and other articles.

Among the articles listed in Table 2, there are only two randomized trials. The other studies consist of observation report, mostly case report or case series with few patients and few studies with medium cohorts. Diversity among these studies hardly allows to bring out any strong conclusion. It is mainly the use of antidepressant among patient with BSD (as defined for each study) that is criticized, while considering mood stabilizer is encouraged. But low level of evidence is a consistent limitation.

The articles in Table 3 are mainly focused on trying to define BSD, to specify symptoms that differ from known mood disorders, and potentially to discuss pharmacological treatment. The subsequent articles, reviews or expert opinion, summarize what is known and encourage an enhanced definition and further research about treatment. While the authors of the first articles are enthusiastic about the concept of BSD, the other authors are more cautious and consider risk of over-diagnosis.

3.3. High-strength evidence findings

Only 2 randomized trials were included. One was a double blind controlled study, while the other one was an open label and only rater blinded study. These 2 studies used different definitions of BSD, different study design and reported on different treatments. The disparity among studies and the lack of consensus on the definition of BSD limits the possibilities of finding evidences for BSD treatment. Patkar et al. (2015) performed a double blind RCT to study the efficacy of ziprasidone among 49 MDD patients positive for at least three predictors of bipolarity (family history of bipolar disorder, antidepressant induced mania, highly recurrent depressive episodes (>5), atypical depression, early onset of depression (<age 20), failure to respond to antidepressants or antidepressant tolerance.) These features of bipolarity in a MDD sample were used to define a BSD. Ziprasidone did not statistically differ from placebo while side effects were significantly higher. This study shows that ziprazidone is not indicated in this condition. It is the only RCT study focusing on this challenging specific population. The choice of ziprasidone is quite astonishing: it is neither a choice treatment in classical bipolar disorder (Yatham et al., 2018) nor for MDD (Kennedy et al., 2016).The study was directly funded by a pharmaceutical producer. Gao et al. (2018) compared quetiapine instant release and lithium in terms of safety, tolerance and efficacy in an open label, randomized and rater-blinded trial. Of the 42 patients with mainly BPI or BPII, only two had been diagnosed with subthreshold bipolar disorder. Subthreshold bipolar disorder was defined as any of the three following: (a) recurrent subthreshold hypomania (> 2 criterion B symptoms and all other criteria for hypomania according to DSM 4) in the presence of intercurrent major depressive episode (MDE), (b) recurrent hypomania in the absence of recurrent MDE with or without subthreshold MDE or (c) recurrent subthreshold hypomania in the absence of intercurrent MDE. Lithium and quetiapine were effective for the patients, which is consistent with what is known about treating bipolar disorder. Efficacy of lithium and quetiapine is already recorded in BPI and II for depression, mania, hypomania and maintenance (Yatham et al., 2018). This study provides clinical comparison between the two mood stabilizers. But it does not provide any evidence about subthreshold bipolar disorder. There is no information about the evolution of the two patients with subthreshold bipolar diagnosis. It is only

Table 2
Summary of included trials.

Study	Design, setting	Participants	BSD definition	Intervention description	Findings
Akiskal et al. (2005)	Observational study	$n = = 254$ MDD	Agitated, activated, or otherwise excited depressions (which the authors consider as depressive mixed states)	Comparison between agitated and non-agitated depressions	Antidepressant monotherapy is inappropriate for agitated depression.
Bisol and Lara (2010)	Case serie	$n = = 4$	Hyperthymic / irritable / cyclothymic temperament or cyclothymic disorder that fail to meet DSM-IV criteria for bipolar I / II or personality disorder	Quetiapine 50–75 mg/daily	Low dose of quetiapine may have therapeutic effects on BSD.
Chaime et al., (2014)	Case report	$n = = 1$	Patient with substance use disorder, pathological gambling and euphoric temperament.	Adding lithium to fluoxetine 40 mg [Li] = 0.5 mmol/L	7 evaluations over 18 months showed less mood instability, irritability and better self-control in gambling. Relapse after stopping lithium.
Kocbiyik et al. (2016)	Case report	$n = = 1$	Patient diagnosed with "bipolar mood disorder, unspecified type" according to DSM 5 criteria because of her symptom onset during adolescence, atypical features of her depressive episodes, chronicity of symptoms, psychomotor agitation, and her hypomania like symptoms, which do not completely meet the diagnostic criteria.	Valproate	Mood enhanced under valproate while moclobemide and lamotrigine did not succeed. Lithium was not tolerated.
Deltito (1993)	Case serie	$n = = 3$	"Bipolar spectrum temperamental disorder": hyperthymic temperament and cyclothymic temperament	Valproate (375–750 mg/daily) +/- lithium	Valproate may be a safe and effective treatment.
Gao et al. (2018)	Randomized open-label, rater blinded trial (pilot study)	$n = = 42$ 25 BD1 15 BD2 2 ST	Subthreshold BD was defined as any of the following: (1) recurrent subthreshold hypomania (≥ 2 criterion B symptoms and all other criteria for hypomania according to DSM-IV) in the presence of intercurrent MDE, (2) recurrent (≥ 2 episodes) hypomania in the absence of recurrent MDE with or without subthreshold MDE, and (3) recurrent subthreshold hypomania in the absence of intercurrent MDE with or without subthreshold MDE	Tolerability and efficacy of lithium $n = = 18$ vs quétiapine $n = = 24$; 2 ST patients received quetiapine	16 weeks study; Minimal difference in reducing depressive, manic and anxiety symptoms and improving quality of life
Goto et al. (2011)	Observational study	$n = = 46$ 1 BD1 9 BD2 36 MDD	Soft bipolar included patients with criteria for bipolar 2, bipolar 2.5 (depression and cyclothymic temperament) and bipolar 4 (depression and hyperthymic temperement). Patients could answer to several diagnosis.	Temperament was assessed for all patients and drug response was investigated using rate of remission (HAM-$D \leq 7$); Treatments were Lithium, valproate, carbamazepine and antidepressants	Among 39 patients considered with soft bipolar, remission rate was higher for those taking lithium. Patients with SSRI had lower remission than those without. All patients with lithium and SSRI were in remission.
John and Sharma (2009)	Case report	$n = = 1$	Ghaemi's criteria (2002).	Quetiapine 300 mg/daily and lamotrigine 200 mg/daily	Lamotrigine and quetiapine without antidepressant result in sustained euthymia.
Ng et al. (2008)	Case serie	$n = = 10$ Elderly patients with late-onset mood and related behavioral symptomatology and cognitive decline without past history of clear-cut bipolar disorder	Mood symptoms in the absence of clear-cut personal history of premorbid BD1 or BD2.	Lithium; Anticonvulsant (Lamotrigine); New generation antipsychotic (Olanzapine, quetiapine)	Mood stabilizers and/or atypical antipsychotics could promote emotional and sometimes cognitive improvement
Patkar et al. (2015)	RCT double blind	$n = = 49$	MDD and 3 predictors of bipolarity: family history of bipolar disorder, AD-induced mania, highly recurrent depressive episodes (>5) (72.3%), atypical depression (52.9%), early onset of depression (<age 20), failure to respond to AD (73.5%), AD tolerance (75%).	Ziprazidone vs placebo. 52% ziprasidone in monotherapy and 48% associated with AD.	No significative difference between ziprazidone and placebo in treating depression among these patients.

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Table 2 (*continued*)

Study	Design, setting	Participants	BSD definition	Intervention description	Findings
Phelps and Manipod (2012)	Case serie	$n = = 12$	Authors suggests that anxiety among patients with MDD with no improvement under antidepressant could be a sign of BSD.	12 patients receiving AD without improvement were included AD was stopped and meanwhile, lamotrigine ($n = = 8$) or lithium ($n = = 3$) was introduced.	All patients with mood stabilizer did improve. Conclusions consists mainly in questions. Was it undiagnosed BD? Do MS have an effect on anxiety? Was it only about treating the depression?
Rybakowski and Kaminska (2008)	Case report	$n = = 5$ Comorbid BSD and bulimic disorders patients	Diagnose of bipolar spectrum is based on the Mood Disorder Questionnaire (MDQ).	Lamotrigine 100–200 mg/daily	Lamotrigine could be efficient in comorbid bulimic and affective disorders.
Sharma et al. (2005)	Observational study	$n = = 61$ Patients with diagnosis of ‘‘unipolar’’ treatment resistant depression	Ghaemi's criteria (2002)	Follow up for at least one year. Prospectively collected data including the occurrence of episodes of hypomania, and supplemental information from family members on illness course	Majority of cases of unipolar treatment resistant depression, occurring in the context of loss of antidepressant response, have a bipolar diathesis. Mood stabilizers and/or atypical neuroleptics were introduced at follow-up for two-thirds of patients who had been taking AD at the time of initial consultation.
Tavormina (2013)	Case serie	$n = = 30$	Author defines mixed states sub-group as irritable cyclothymia, mixed dysphoria and agitated depression.	Different polypharmacology for each patient. Mixing antidepressants, mood stabilizer and antipsyhotic. All patients had an AD.	Benefits were assessed using evolution of GHI over 2 years. Gabapentin was the most used mood stabilizers for its tolerability and effectiveness.
Wang et al. (2014)	Case report	$n = = 1$	Depression with hypomania < 4 days	Divalproate and quétiapine	Improvement in mood and in pedophilia

MDE: major depressive episode.
MDD: major depressive disorder.
BD: bipolar disorder.
BSD: bipolar spectrum disorder.
AD: antidepressant.
RCT: randomized controlled trial.
ST: subthreshold.

Table 3
Summary of other included studies.

Study	Design	BSD definition	Intervention description	Findings
Akisakal and Mallyal (1987)	Expert opinion	Recurrent tendency to hypomanic excursions coupled with depressive periods of varying duration and severity.		Caution in the overzealous use of tricyclic antidepressants.
Benazzi (2003)	Prospective study	MDE with anger.	Assess whether MDE with anger is closer to bipolar II disorder or to MDD.	Anger associated MDE happens more among bipolar patients (62% BD2 *versus*35.6% MDD).
Benazzi (2003)	Prospective study	Focus on family history among patient with depression.	Characteristic comparison of patient with BD2 and unipolar depression with or without family history of bipolarity.	Unipolar depression with family history of bipolarity shares more with BD2 than with unipolar depression without family history of bipolarity, suggesting it could be included in the BSD.
Benazzi et al. (2004)	Prospective study	Mixed depression, meaning MDE and > 2 excitatory signs - Inner psychic tension (irritability) - Psychomotor agitation - Racing/crowded thoughts	Comparison between unipolar and bipolar depression; $n = = 336$ (206 BD2 and130 MDD)	The highest rate of mixed depression (38.6%) was achieved with a definition combining MDE with psychic tension (irritability) and crowded thoughts: 23.0% of these belonged to MDD and 76.9% to BD2.
Benazzi (2004)	Prospective study	Study about agitated depression: MDE associated with psychomotor agitation. Mixed agitated depression = MDE and more than 4 hypomanic symptoms	Determine agitated depression; $n = = 434$ (245 BD2; 189 MDD); Inclusion over 4 years	34% AD; Mixed agitated depression = 70% of AD; Association between AD and bipolar validators; Questions this entity since antidepressant could increase agitation.
Correa et al. (2010)	Review	Classic conceptualization and broadly defined "soft bipolar spectrum" (Akiskal, 1986, Akiskal and Malltya, 1987).	Review seeking for data suggesting that treatment resistant depression could suggest BSD.	Limited data to support the hypothesis.
Dorey et al. (2008)	Review	Description of the different concepts of BSD.	Review of BSD and explain behavioral and psychological symptoms of dementia before proposing clinical pointers of a possible BSD contaminating the phenomenology of dementia.	Some behavioral and psychological symptoms of dementia could be the common clinical expression of both dementia and an undiagnosed comorbid bipolar spectrum disorder. Targeted prescription of mood-stabilizing agents in lieu of AD monotherapy.
Dunner (2003)	Review	Schizoaffective bipolar disorder, BD1, mixed states, BD 2 (and possibly bipolar II mixed states), hypomania occurring during treatment of depression, cyclothymia, hyperthymic temperament, depression occurring in the context of a positive family history of mania, and brief (<4 days) periods of hypomanic symptoms.		Pharmacological agents with mood-stabilizing properties form the foundation of options.
Ghaemi et al. (2002)	Review	*Cf supra.*	New definition for BSD. Review of the role of antidepressants.	Association between antidepressant use and rapid cycling. Such an association argues for caution in using AD to treat BD, limiting them to severe acute depression and generally stopping them in long-term maintenance treatment.
Gilmer (2001)	Expert opinion	BD1 and 2, cyclothymia, bipolar disorder NOS, brief recurrent hypomania, antidepressant-induced hypomania/mania, subsyndromal mixed mood states, recurrent depressions with hyperthymic temperament.	Review of the available efficacy data anticonvulsants.	Anticonvulsants (carbamazepine, oxcarbazepine, valproate, lamotrigine, gabapentin and topiramate) may be in treatment of mood conditions other than acute mania.
Katzow et al. (2003)	Expert opinion	Patients with non-classical bipolar features.	Clinically oriented paper.	While antidepressants may be useful in particularly difficult cases, emphasis should be placed on mood stabilizers for treatment of the BSD.
Manning et al. (2002)	Expert opinion	BD1, BD2, depressions with possibly pharmacologically mobilized hypomania, cyclothymic disorder ("minor" depression and hypomania), depression arising from temperamental hypomanic traits, depression on a cyclothymic temperamental baseline, and periodic depression responsive to mood stabilizers.		To discontinue the AD prior to instituting a mood stabilizer or add the mood stabilizer to the AD.
Mitchell (2012)	Expert opinion	Criticize the lack of clear definition.	Questions the broadening of bipolar disorder.	Emphasize the need to clarify what BSD is. very heterogeneous population .Hardly no data about efficacy of treatment of "BSD, also with burden of wrong diagnosis, wrong treatment, etc. … Also criticize the link between Drug resistant depression and bipolar spectrum disorder (cf. Perlis et al., 2011), while Correa et al., 2010 still support it even with lacking data.
Muzina (2007)	Review			General treatment principles for BD, not for BSD.

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Table 3 (*continued*)

Study	Design	BSD definition	Intervention description	Findings
		Any highly recurrent mood disorder characterized by instability of affect, energy, or behavior that is not classically should be considered as potentially within a BSD.	Review the epidemiology and diagnostic characterics of BD and BSD and provide an overview of the treatment of BD.	
Paris (2014)	Expert opinion	"Subclinical phenomena", when criteria for hypomania is not met. Criticize the lack of clear definition.	Questions the BSD.	No evidence data about treatment.
Patten and Paris (2008)	Review	Search using "Bipolar Disorder" and "Spectrum" keywords then looking for treatment study, completed with search for articles citing Ghaemi et al. (2002).	Looking for outcomes associated with altered diagnostic practices	No RCT was found.
Piver et al. (2002)	Review	Spectrum of conditions characterized by hyperthymic mood states, including - type III (depressive episodes with AD-induced hypomanic episodes); - type IV (depressive episodes with premorbid hyperthymic temperament, ie hyperthymic mood persisting for several years as a baseline mood state punctuated by episodes of depression); - and cyclothymic disorder (chronic, frequent shifts from mild hypomania to mild depression without an extended [2-month] period of normal mood).There might also be "soft" bipolar features, such as recurrent but brief hypomanic episodes lasting less than 4 days.	Review perspectives on diagnosis, clinical features, epidemiology, and treatment of BD2 and related disorders	Mood stabilizers, adjunctive medications, and judicious use of AD.
Smith et al. (2010)	Expert opinion	Unipolar depression with mild or brief episodes of hypomania which fall below the threshold for a formal BD.	Perspective of BSD seen from the primary care point of view.	Patients seen in primary care, mostly when depressed. High rate of depression and lack of response to AD. Should it lead to lamotrigine or quetiapine like bipolar depression?
Strakowski et al. (2011)	Expert opinion	About broadening the actual definition of BD.	Discusses risks and benefits of broadening BD diagnosis.	No data demonstrating any usefulness of using bipolar treatment instead of depression treatment guidelines for patients with depressed BSD.
Zimmerman (2012)	Expert opinion	Broadening classical bipolar definition.		Risk of overdiagnose. No evidence for evolution of soft bipolar toward true bipolar disorder. No evidence about treatment usefulness.

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specified that they both received quetiapine. Future research focusing specifically on subthreshold patients would be required.

4. Discussion

4.1. What is BSD?

The ambiguity around the BSD concept has been highlighted over the last 10 years. In 2012, Mitchel pointed out the need to clarify what this diagnosis is. Paris (2014) also reported on the lack of validity of the diagnosis. Lack of precision in the criteria for BSD has been iteratively criticized without clarification over a decade. Concepts of non-otherwise specified, other specified or unspecified bipolar disorder feed this blur. The contrast between classical bipolarity which responds to clear definition and all entities qualifying for unspecified bipolarity is profound. Are we discussing same entities when talking about BSD? Of course, the concept of "spectrum" implicates a variety of clinical presentation. However a logical or clinical link is needed to aggregate different conditions together. The disparity of definitions of BSD is prominent when looking among the studies included in our review. Although most of the studies included patient with depressive episode at some point in the course of the disorder, BSD comes with additional symptoms that involve various aspects. Some studies included behavioral descriptions such as agitation (Akiskal et al., 2005) or bulimia (Rybakowski and Kaminska, 2008), subthreshold hypomania (Wang et al., 2014; Kocbiyik et al., 2016; Gao et al., 2018). Others included symptoms of mixity (Tavormina, 2014), concept of temperament (Bisol and Lara, 2010; Deltito, 1993; Goto et al., 2011; Chaim et al., 2014), anxiety (Phelps and Manipod, 2012), substance use disorder (Chaim et al., 2013), or personal and family history (John and Sharma, 2009; Sharma et al., 2005; Patkar et al., 2015) … Our review emphasizes that there is still no consensual definition of BSD. In 2013, the DSM-5 did not mention the concept of BSD which did not allow the clarification of the definition of the concept. Ghaemi's definition (2002) seems to be the most frequently used, probably because it is the most exhaustive. Indeed, his heuristic definition takes into account different features of BSD: family history, temperaments, clinical characteristics of the depressive episodes and psychopharmacological issues (switch, resistance). It is a large compromise that puts the focus on evolving conditions. Because of treatment implication or of the course of the disorder, reasons to use such entity should be better explained.

4.2. Pharmacological implications

In spite of the abundance of literature on BSD, there are very few studies assessing its potential treatment. In their review of the literature, Patten and Paris (2008) criticized the lack of data concerning treatments. There was at the time no significant study neither about the BSD nor about its treatment. Zimmerman et al. in 2012 pointed out the same lack of studies when DSM-5 was still being discussed. Nothing had changed in 2014, when Paris showed the lack of evidence about pharmacological treatment of BSD. We found only two RCTs (Patkar et al., 2015; Gao et al., 2018), with small sample size and only two treatments assessed (ziprasidone, quetiapine). None of them gave indication concerning treatment efficacy. Other type of studies did not provide sufficient evidence about treatment either. Even when good results are suggested (Kocbiyik et al., 2016; Wang et al., 2014; Chaim et al., 2014), they were specific to patients with significantly different clinical presentations. The patients among these case reports or series responded to different definition of BSD. There is still unfortunately no sufficient data to establish guidelines with high-strength evidenced-based recommendation to treat BSD.

A preliminary question could be what is being treated? Concerns about bipolarity and interest for mood stabilizer often appears after facing resistance to antidepressants which are not recommended in this condition. Francesca et al. (2014) retrospectively reviewed files of 466 patients with treatment-resistant depression (TRD) and found that 57% were positive on the hypomania checklist-32 items (HCL-32, Angst et al., 2005) and 11.6% met the DSM-4 bipolar disorder criteria. This emphasizes the need to screen for bipolar disorder in all patients with MDD. Psychiatrists should be aware of that, but repeating it will never be superfluous. In primary care, screening for depression is recommended (Joffres et al., 2013) and many patients show lack of response to antidepressants leading to think about an unrecognized bipolar disorder (Manning et al., 2002; Smith et al., 2010). While the HCL-32 and/or the MDQ are helpful screening tools to assess BD, clinical evaluation remains absolutely necessary to confirm a BD diagnosis before prescribing mood stabilizer (Paterniti and Bisserbe, 2018). These patients should always be addressed to psychiatrists for deeper exploration. Lack of response to antidepressant therapy is not rare (Bschor and Kilarski, 2016), and is not enough to diagnose neither BD nor BSD. Correa et al. (2010) reviewed 196 articles and did not find sufficient evidence to consider TRD as a sign of bipolarity. Perlis et al. (2011) did not find evidence that symptoms of bipolarity among patients with major depressive disorder leads to resistance to antidepressant (Perlis et al., 2011) and molecular measure of genetic susceptibility to BD has not been found among patients with TRD (Tansey et al., 2014).

Clinical presentation of depression is another key in suggesting bipolarity. Link between agitated depression and BSD has been emphasized in several study (Benazzi, 2003a,b; 2004, Benazzi et al., 2004; Verdolini et al., 2014) showing that patients with agitated depression do share more validators with bipolar disorder (BD) than with unipolar disorder (UD). Mixed feature among depressed patients (Ferentinos et al., 2017) or aggressiveness in depression (Verdolini et al., 2017) were also considered as a sign of bipolarity in these studies, even though classical bipolar disorder could not be diagnosed. Akiskal et al. (2005) pointed out that use of antidepressants among these patients may be inappropriate and could worsen agitation. There is a lack of evidence to confirm that risk and to recommend not to use antidepressants. Several studies tend to minimize concerns about use of antidepressants for bipolar II patients given the effective response rate with antidepressant monotherapy (Parker et al., 2006; Amsterdam et al., 2015). Some authors suggested a link between symptoms intensity and disorders intensity and proposed treating these "soft patients" with "soft treatments". In their case series, Bisol and Lara (2010) used temperament as diagnosis criteria and showed that low doses of quetiapine may have therapeutic effects on mood, emotional regulation and sleep. In a case report, John and Sharma (2009) reported that differentiating borderline personality disorder from BD is challenging in the clinical setting because of the overlapping symptoms between the two disorders such as affective instability and impulsivity. Thus, when there is suspicion of a bipolar diathesis, it is suggested that antidepressants monotherapy should be used with caution or in combination with mood stabilizers and/or neuroleptics. Similarly, in elderly patients suffering from dementia and mood symptoms, antidepressants and acetylcholinesterase inhibitors may be ineffective or even harmful whereas mood stabilizers and/or atypical antipsychotics are beneficial (Ng et al., 2008). Lack of response to a treatment or response to a treatment are not enough to make diagnosis. Sedative properties of quetiapine may be effective on symptoms of many psychiatric disorders, and lithium, quetiapine or aripiprazole are used as adjunctive treatment for resistant depression. Treatments should rely on current guidelines. Antidepressant are first line treatment for all depressions. Sedative or anxiolytic drugs can be associated when necessary.

4.3. Consequences of such a diagnosis

The recognition of BSD has to improve in order to improve its treatment and management. Is BSD a pre-onset stage for bipolar I or II? Clinical diagnostics are not unchanging and can evolve in time. Woo et al. (2015) explored in a retrospective study, the conversion from

UD to the different BD. The diagnostic conversion from MDD to BD was observed in 18.4% of 250 MDD patients, during 5 years. A family history of BD, antidepressant-induced mania/hypomania, brief major depressive episodes, early age of onset, antidepressant wear-off, and antidepressant resistance were independent predictors of this conversion (Woo et al., 2015). In a recent meta-analysis nearly a quarter of adults (22.5%) and adolescents with MDD followed up for a mean length of 12–18 years developed BD (Ratheesh et al., 2017). The greatest risk of transition was in the first 5 years of follow-up. This meta-analysis identified that transition from MDD to BD was predicted by family history of BD, earlier age of onset of depression and presence of psychotic symptoms. Recently, an historical prospective cohort study based on 91 587 individuals diagnosed with UD in Danish hospital psychiatry between 1995 and 2016 reported that during follow-up 3910 individuals with UD developed BD (Musliner and Østergaard, 2018). The cumulative incidence of conversion was slightly higher in females (8.7%) compared to males (7.7%). The strongest predictor of conversion from UD to BD was parental history of BD. Other predictors included psychotic depression at the index UD episode, a prior/concomitant non-affective psychosis, and in-patient treatment at the index episode.

There is not precise data about conversion from BSD to classical BD. MDD is the main common point in most BSD classified situations. In studies exploring conversion from UD to BD, the diagnostic conversion from UD to BD is predicted by clinical features listed in the criteria used by Ghaemi et al. (2002) to define BSD. The rate of conversion from MDD to BD is not constant and seems to decrease with time: 3.9% in the first year after study entry with UD to 3.1% in years 1–2, 1.0% in years 2–5 and 0.8% in years 5–10 (Kessing et al., 2017). In summary, Ghaemi's criteria seem to be efficient predictors of conversion risk from UD to BD. Moreover, the rate of conversion is higher in the first years of the disease. Risk factors and prodromes are crucial since delayed and incorrect diagnoses are common in BD. The available observations invite to consider Ghaemi's criteria of BSD as predictors that should be checked in patients with depression. This process is quite similar with bipolar not otherwise specified (NOS) diagnose. NOS and “subthreshold bipolar disorder” are often selected when criteria for bipolarity are not fully achieved. No specific treatment is involved, but these conditions appear to be warning signs.

In this study, we focused on BSD as defined by Ghaemi because it is probably easier to operationalize for clinicians. Other authors (Alloy et al., 2006a,b; 2012; Sperry and Kwapil, 2017; Walsh et al., 2015) provided evidence that it may be possible to identify individuals at risk for initial onset of BSD based on various measures (such as the behavioral approach system (BAS), the hypomanic personality scale (HPS), or the use of experience sampling methodology (ESM) to capture bipolar spectrum psychopathology (BSP)). These measures identity features of the heterogeneity that exists in BSD and aid understanding risk and protective factors. The clinical implications address the question of early intervention. It may be possible to intervene early to prevent onset of bipolar disorder, or to at least lessen the severity of the disorder's course. Jablensky (2016) discussed the fact that most diagnostic concepts in psychiatry have not been demonstrated to be valid, meaning they did not show to be discrete entities. Clinicians prefer to hold on to the categorical approach embodied in current classifications such as ICD-10 (WHO, World Health Organization, 1992) and DSM-5. Researchers are increasingly more likely to adopt a continuum/dimensional view of the variation in symptomatology. Jablensky (2016) concluded with the idea that “our primary concern should be the progressive refinement of the utility of the diagnostic concepts and tools, towards the enhancement of their phenomenological accuracy, predictive value and capacity to guide person-focused treatment and management decisions », therefore giving space for a reconciliation between both points of view.

The main limitation of our review is the exhaustivity. We led this research through two major databases but possibly did not access to studies published elsewhere. However, it is unlikely that RCTs and meta-analyzes about the BSD are not referenced in MedLine / PubMed database, among others. As a result, the fact that we have not worked on other databases should not influence our conclusions. Secondly, we focused specifically on pharmacological treatments, and did not take into account other therapeutic approaches such as psychological or psychosocial interventions. These interventions may be relevant for “subthreshold” disorders.

5. Conclusion

Based on the available data, we cannot conclude regarding pharmacological treatment to patients considered to suffer from BSD. No randomized clinical trial shows that psychopharmacological interventions known to be effective for BD I or II are also effective for BSD. Caution about making such a diagnosis is required. This kind of diagnoses always have clinical and therapeutic implications and psychosocial consequences. There is a real need for a consensus on the definition of BSD. Ghaemi's definition seems to be the most effective. It takes into account different and various features of BSD (family history, clinical characteristics of the depressive episodes psychopharmacological issues, *etc.*); and most of these criteria are predictor of conversion from UD to BD. If we consider a continuum between normal mood variations and clear BD, with BSD in-between, then the discussion is about what to treat and how. It is not about trying to define a new category. Pursuit of a validated definition of BSD and the description of a coherent definition will allow studies to then focus on clarifying the specific medication, the risk of evolution toward BD and if a pharmacological treatment can protect against evolving into a more severe state.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

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