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SYSTEMATIC REVIEW OPEN ACCESS

Treatment of Early-Onset Specified and Unspecified Bipolar Disorders: A Systematic Review and Strategies for Identifying and Managing a Thermally Dysregulated Subtype in Children

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ABSTRACT

Introduction: Bipolar disorder (BD), characterized by extreme mood shifts between mania and depression, can manifest in childhood, and pose treatment challenges. Treatment for full-criteria BD I or II in children has been partially described in the literature, but major uncertainties exist regarding non-classic presentations, which were originally designated as bipolar "not otherwise specified" (BP-NOS) in DSM-IV and in DSM-5 and ICD-11 as either other specified or unspecified BD (S-USBD). This review aims to provide literature-based recommendations on the treatment of S-USBD, with a focus on a fear of harm (FOH) subtype, now termed temperature and sleep dysregulation disorder (TSDD).

Methods: A broad systematic literature review with AI assistance was conducted to identify all articles in PubMed providing data on the treatment of children with either atypical BD, BD-NOS, USBD, specified BD, rapid cycling BD, or a phenotype of BD.

Aims: Given the paucity of pharmacological treatment literature on any of the earliest forms of BD prior to their achieving a BP I or BP II diagnosis, it was felt that there was a critical need to review the existent literature on the earliest presentations and prodromes, which now fall under the rubric of specified (BD S-USBD). Here, the focus is on the prevalent BP-NOS subtype, which meets all the classical presentations of BP except for the brief durations of mania, and a more newly recognized form of S-USBD called TSDD.

Results: Eleven family-focused psychotherapy studies were identified, including nine randomized controlled trials (RCTs) with uniformly positive results versus the comparative group, which was treatment as usual (TAU) for unclear subtypes and subtypes of S-USBD. Only three psychopharmacological RCTS were reported, and only one on aripiprazole in unspecified subtypes of S-USBD in high-risk children showed a significant difference from placebo. None of the controlled trials and only two case series provided separate outcome data on the S-USBD subtypes, except for one that focused exclusively on the TSDD subtype. These two case series reports preliminarily defined the TSDD subtype and provided novel pharmacological treatment data, including lithium, clonidine, and ketamine, which led to good outcomes.

All listed authors have contributed to the manuscript substantially and have agreed to the final submitted version.

Conclusion: Good support was provided in the 11 studies for the use of adjunctive family-focused psychotherapeutic approaches, and this approach should be considered an important part of any treatment regimen. The pharmacological treatment landscape for S-USBD lacks a systematic research base, warranting further exploration with controlled clinical trials. Case series indicate promising treatment outcomes for TSDD with high-dose lithium, clonidine, ketamine, and other cooling measures. Validation of this novel treatment strategy in controlled trials is needed to advance the management of the S-USBD variants.

1 | Introduction

Given the paucity of pharmacological treatment literature on any of the prodromal forms of bipolar disorder prior to the onset of BP I or BP II diagnosis, it was felt that there was a critical need to review the existing literature on the earliest presentations and prodromes, which now fall under the rubric of other specified or unspecified BD (S-USBD). Here, the focus is on the prevalent BP not otherwise specified (BP-NOS) subtype, which meets all the classical presentations of BP except for the brief durations of mania [1], and a more newly recognized form of S-USBD called temperature and sleep dysregulation disorder (TSDD). Prior diagnostic, therapeutic, and prevalence studies of childhood-onset BD have centered almost exclusively on youths meeting full criteria for BP I and BP II disorders. Kowatch et al. [2] reviewed consensus recommendations for acute treatment of BP I mania (which included mood-stabilizing anticonvulsants, atypical antipsychotics, and lithium) and on prophylaxis, but even in this instance, the recommendations were based more on clinical experience than on controlled clinical trials. More recently, Hobbs et al. [3] provided detailed algorithms for the treatment of mania, depression, and mixed episodes in youths exclusively with BD I, which were based primarily on clinical trials and Food and Drug Administration (FDA) approval. Likewise, Ratheesh et al. [4] dealt with only those meeting criteria for BD I or II and excluded consideration of those with S-USBD or BP not otherwise specified (BP-NOS), so there seemed to be a great need for a systematic review of possible treatments for these large groups of children who are often those afflicted with the earliest and most severe prodromal forms of the illness.

A focus on these earliest manifestations of BP spectrum illness prior to their development in a full-blown form would be of great importance, since the review of Ratheesh et al. [4] of the early but already fully manifest forms of BD provided highly suggestive data that earlier treatment was more effective than later treatment with lithium and several other agents. Thus, there is a great unmet need to discern what might be the most effective interventions in those at high risk or with prodromes to prevent or delay the onset of full BD. A major contribution of the current systematic review in S-USBP is the revelation of the paucity of systematic data in the literature to guide clinical interventions with pharmacotherapy. At the same time, there is a modicum of promising data on the likely effectiveness of a variety of family and individual psychotherapeutic approaches to these early forms of BP.

Epidemiological studies suggest that about 1.8% of children (age 7–21) meet full diagnostic criteria, which require a minimum duration of 4 days of hypomania for BD II and a week or more of mania for BD I [5]. However, the subtype of BD-NOS was not included in these assessments. When BD-NOS is included, prevalence rates can increase to 3%–6%. Merikangas et al. [6] reported a 2.9% prevalence of BD I and II in the United States, with severe impairment in 2.6%, but there was a distressingly low percentage of children who were in any kind of treatment. There is also considerable evidence that there is a higher incidence of early childhood- and adolescent-onset BD in the United States compared to many European countries [7–9], making the need for new intervention studies even more pressing.

2 | Aims of the Study

The aim of this broad systematic review is to synthesize the current literature base examining data on the treatment of children with either atypical BD, BD-NOS, USBD, specified BD, rapid cycling BD, or a phenotype of BD.

2.1 | Diagnostic Controversies

There has been some controversy about what criteria are required to meet the diagnosis of childhood-onset BD. Liebenluft et al. [10] have taken the position that there must be a clear-cut duration of episodes that conform to adult criteria of BD I or II and excluded those with rapidly fluctuating mood states as not part of a "narrow definition," but instead falling within a "broad definition" of BD [11]. This latter category was thought to include those with severe mood dysregulation (SMD) that was not associated with a high incidence of a positive family history of BD, but was more likely to evolve into anxiety or depressive disorders in adolescents and young adults [12]. In one small study, children categorized with SMD (now called disruptive mood dysregulation disorder or DMDD) had chronic hyperactivity and high levels of irritability and were unresponsive to lithium [13]. Based on indirect inferences, these individuals were thought to respond well to stimulants and antidepressants. Biederman et al. [14] also recognized that there was a group of children who might not meet the criteria for BD as they did not exhibit clear mania with euphoric or irritable moods as defined in adults, but instead were likely to have attentional control problems, severe chronic irritability, deficits in emotional regulation, and behavioral dyscontrol.

Axelson et al. [15] and Birmaher et al. [1], in the extensive ($N = 413$, age 7–17) *Course and Outcome of Bipolar Youth* (COBY) study, described three subtypes of children with BD. The largest group was those with BD I ($n = 244$). At the same time, 141 were labeled BD-NOS and met the same criteria as BD I or II ($n = 28$) groups, but with shorter manias below threshold duration for adult BD [1]. "Bipolar-NOS was characterized by rates of comorbidity, suicidality, functional impairment (except hospitalizations), and family history for mood disorders equivalent to bipolar-I and II groups." They found that the BD-NOS group had an earlier age of onset, was almost as severely impaired as

Summary

- Summations
  - There is a substantial literature on the efficacy of adjunctive family-focused psychotherapeutic approaches in specified or unspecified bipolar disorder (S-USBD), suggesting this should be part of the standard of care.
  - Although S-USBD can be severe and highly debilitating, there are minimal systematic data focused on this subtype's pharmacological treatment.
  - A large case series suggests that a subtype of S-USBD called temperature and sleep disruptive disorder (TSDD) may respond well to novel manipulations aimed at heat dissipation.
- Limitations
  - Different subtypes of S-USBD require more systematic diagnostic delineation and definition, especially around the issue of consistency of diagnosis and longitudinal trajectory.
  - Pharmacological studies in the spectrum of childhood-onset BD rarely specify results separately for those with S-USBD from those with bipolar I (BP I) or BP II disorder.
  - The novel potential treatment of TSDD with lithium, clonidine, and intranasal ketamine is based on only two case series and needs to be verified in controlled studies.

the BD I or II groups, and took much longer (more than 2 years) to stabilize in comparison to those with BD I or II, who usually stabilized in under 1 year. Some of these youths would now meet DSM-5/ICD-11 criteria for "Other Specified BD with short-duration hypomanic episodes (2–3 days) and major depressive episodes."

When children with BP-NOS were followed prospectively for more than 4 years, about 50% with a positive family history of BD eventually converted to a BD I or II diagnosis [1, 15, 16]. Hafeman et al. [17] developed a risk calculator to estimate which children would convert to BD I or II. Brief periods of euphoria, mood lability, and a parent with an early-onset illness history were recognized as risk factors. Finally, Birmaher et al. [18] reported that polygenic risk scores (PRS) were higher in children with BD and their BD parents than in other groups. Most important for this review was that the PRS were similar in the BD-NOS subtypes to those of BP I and BP II.

These data provide strong evidence that BD-NOS is part of the classic BP spectrum and represents one of the earliest presentations of BD, accompanied by considerable disability and dysfunction.

Leibenluft's [12] characterization of those with SMD eventually led to a more specific definition of DMDD in the DSM-5. However, further study of those who met these criteria suggested that this array of symptoms was nonspecific, and the general syndrome was often seen in association with other diagnoses, including depression, anxiety, oppositional defiant disorder (ODD), attention-deficit/hyperactivity disorder (ADHD), and other disruptive behavioral disorders [19, 20]. One of the motivations for developing the DMDD category was to reduce what, in the opinion of some investigators, was a too high incidence of BD diagnoses in the juvenile population [21, 22]. Problematically, when the DMDD diagnosis was included in the DSM-5, there were no treatment trials to describe the most efficacious treatments. A panel of experts from the World Health Organization's International Classification of Diseases, 11th Revision (ICD-11) recommended that DMDD symptoms be more appropriately classified as an ODD specifier rather than a separate diagnosis. Mayes et al. [23] found that DMDD could not be differentiated from ODD based on symptomatology. Ninety-two percent of children with DMDD symptoms had ODD, and 66% of children with ODD had DMDD symptoms, indicating that it is very unlikely to have DMDD symptoms without ODD, but that ODD can occur without DMDD symptoms. Eventually, the NIMH group did treat some children with DMDD and reported that only 35% responded to the combination of an antidepressant (citalopram) and stimulant (methylphenidate), compared to 6% on methylphenidate alone. Still, many also required a range of other treatments, as the children remained with considerable functional impairment [24].

2.2 | Aims

Given the lack of a systematic pharmacological treatment literature on any of the earliest forms of BD prior to their achieving a BP I or BP II diagnosis, it was felt that there was a critical need to review the existing literature on the earliest presentations and prodromes which now fall under the rubric of S-USBD. In this review, the focus is both on the prevalent and better-known BP-NOS subtype, which meets all the classical presentations of BP except for the brief durations of mania [1], and a more newly recognized form of S-USBD called TSDD [25, 26]. TSDD, in addition to the typical manifestations of BP, has three unique characteristics including fear of harm (FOH) to self and others, profound episodes of hyperthermia, and sleep disturbance with horrendous nightmares. This became a major focus of this review, as this subtype had the best, but uncontrolled, data for novel clinical interventions.

2.3 | Method

A broad AI–guided search of PubMed was conducted using the terms BP, treatment, and adolescent and the terms BP, treatment, and child in all relevant fields. A computer program written in R removed duplicates and articles without abstracts. The program then presented the title of the articles and the abstracts to ChatGPT-3.5-turbo through the API, and asked the following question: "Answer Yes or No only. Does the following article describe the effects of a specific treatment on bipolar disorder?" If the answer was "Yes," the program then asked ChatGPT these two questions: "Answer Yes, No, or Unknown only. Does the article describe the effects of treatment in individuals younger than age 18 years?" and "Answer Yes, No, or Unknown only. Does the article describe the effects of treatment in individuals with either atypical bipolar disorder, bipolar disorder NOS, unspecified bipolar disorder, specified bipolar disorder, rapid cycling bipolar disorder, or a phenotype of bipolar disorder?"

Citations that received three "Yes" responses were placed in one folder, those that received a "Yes" to Question 1 and "Unknown" to one or two of the subsequent questions, and zero "No" responses were placed into a separate folder. A third folder was created for files in which the total token size for the citation, abstract, and questions was likely to exceed ChatGPT-3.5-turbo's token limits. Abstracts and citations in these three folders were then reviewed by hand by DP and RP for inclusion and exclusion. Complete articles were then downloaded for those citations and abstracts with consensus agreement, and results were tabled.

For completeness, a second search was conducted using EMBASE. The methodology was the same, except we filtered citations and abstracts to remove those previously identified in the PubMed search, and ChatGPT-4o-mini was used to select potentially relevant citations using the three previously delineated questions.

2.4 | Results

As illustrated in Figure 1, 11,174 citations were identified through PubMed and culled to 7319 after removing duplicates and citations without abstracts. The AI search reduced the number of citations to 40 probable and 525 possible. Of these, $n = 23$ articles were found eligible following joint review by two of the authors. Eleven family-focused psychotherapy studies were thus identified, including nine randomized controlled trials (RCTs) and three psychopharmacological RCTS.

As illustrated in Figure 2, the Embase search retrieved 4399 citations for children and 764 for adolescents. Three hundred and seventy-eight citations were removed as duplicates. A total of 256 were removed for missing abstracts, leaving a total of 4529 citations. One thousand five hundred and ninety-four of these citations were in the PubMed file and were removed, leaving a total of 1935 novel citations that were processed through ChatGPT-4o-mini. This search identified 40 citations that appeared to meet all criteria and 30 citations that satisfied some criteria and were indeterminate on the other criteria. These 70 citations were reviewed by one of the authors, and he concluded that none of these met our inclusion and exclusion criteria. This was largely because most of these were meeting abstracts and not peer-reviewed articles.

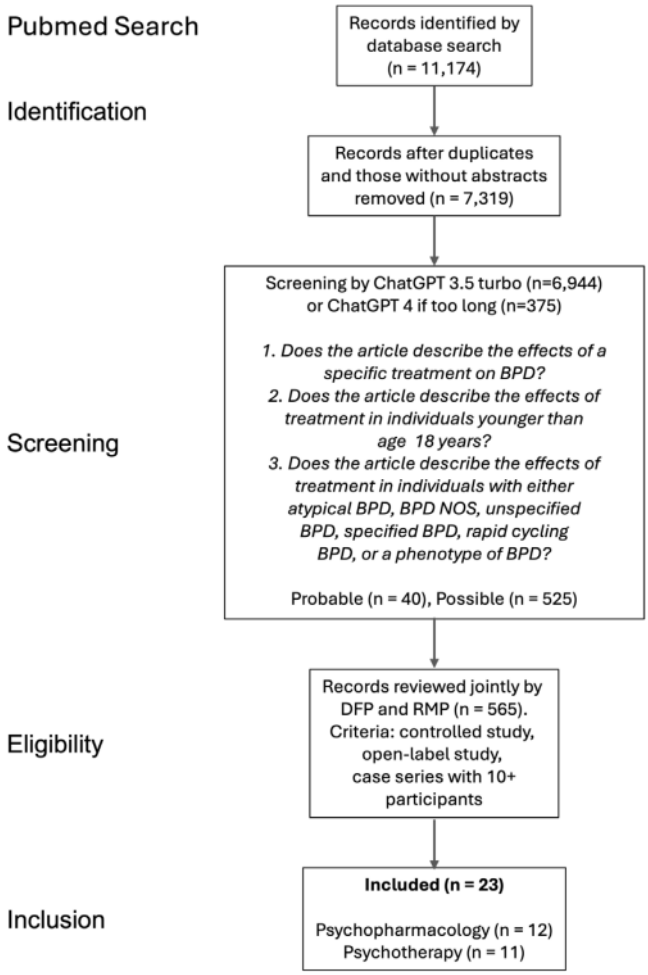


FIGURE 1 | PRISMA flowchart for AI–guided literature search of PubMed.

2.5 | Pharmacological Interventions in Study Populations That Included Children With BD-NOS

There were 12 studies that met our inclusion criteria; only three were RCTs (the remainder were open studies or case reports). One important study that was not included because the cases were treated naturalistically [27], followed a group of children with the entire spectrum of BD (BD I, BD II, and NOS) longitudinally. They found that those who were treated most of the time with lithium had more successful outcomes than those treated with some mood-stabilizing anticonvulsants or atypical antipsychotics. Those on lithium spent less time depressed and made fewer suicide attempts than the other groups.

These non-randomized open follow-up data are highly reminiscent of Geller et al. [28] in their 8-year follow-up of children with BD treated naturalistically in the community. Many of these children showed ultrarapid and ultradian cycling and would very likely have met the later-derived diagnosis of BD-NOS. Geller et al. [28] found that 47% of these well-diagnosed children were never treated with any of the medications considered appropriate for BD, that is, lithium, a mood-stabilizing anticonvulsant, or an atypical antipsychotic. However, those treated with lithium fared the best and had the longest time in remission.

In one of the few randomized but open treatment trials of children with BD, Geller et al. [29] reported that risperidone was more effective than lithium or valproate, and upon re-randomization, those who had risperidone in the regimen again did the best. However, risperidone had more sedative side effects, and there were major differences in efficacy by site. In a placebo (PBO)-controlled study, Findling et al. [30] found that lithium was efficacious in BD I mania, although children with S-USBD were not included in that study.

In DSM-5 and ICD-11, the diagnosis of BD-NOS was discontinued. Instead, several variants were specified, including short-duration hypomanic episodes (2–3 days) and major depressive episodes; hypomanic episodes with insufficient symptoms and major depressive episodes; and hypomanic episodes without a

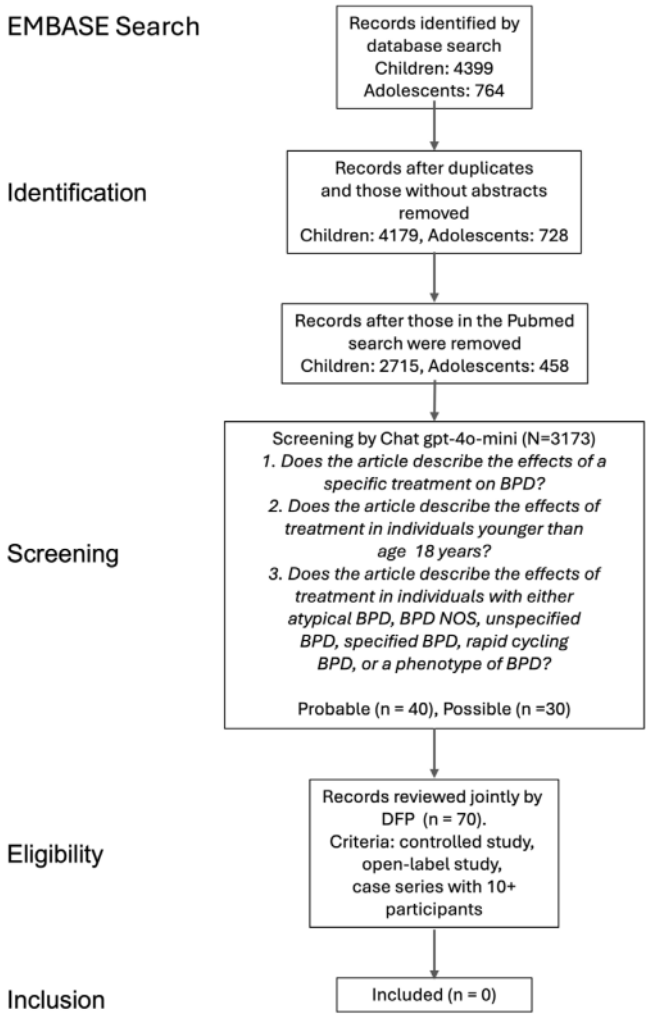


FIGURE 2 | PRISMA flowchart for subsequent AI–guided literature search of EMBASE.

prior major depressive episode. In addition, a new category of USBD was created to label cases in which symptoms characteristic of a BP and related disorders were present that cause clinically significant distress or impairment but do not meet the full criteria for any of the disorders in the BP and related disorders diagnostic class. This category was largely reserved for situations in which the clinician chose not to specify the reason that the criteria were not met and includes presentations in which there is insufficient information to make a more specific diagnosis, such as in an emergency room setting. Unfortunately, the only non-classical variant of BD that has been rigorously defined [1, p. 27636] (Birmaher and Axelson [31], p. 6359) and carefully researched, which was referred to as BD-NOS, was not included as an Other Specified variant, possibly because it included children with brief periods of mania (as short as 4 h/day during 4 consecutive days). However, these children meet all the other criteria for BD and have high rates of conversion to BD I or II [1, p. 27636, 129]. This is the form of the condition that has been described as ultrarapid or ultradian (within the day) cycling in the classical literature (Kramlinger [32], p. 118).

Table 1 includes the pharmacological studies meeting our literature search criteria for the group of children characterized under the rubric of BP-NOS or S-USBD and other aspects of the BP spectrum, including cyclothymia. This combined group will be referred to for convenience as USBD.

Only three controlled studies focused exclusively on the group meeting our selection criteria for USBD. These included: Findling et al. [35], and Findling et al. [34]. McNamara et al. [33] compared fish oil 2100 mg/day to PBO for 12 weeks and found that it was not superior to PBO on the CDRS-R. The control group was most often treated as usual and rarely included a formal PBO arm, but was based on a clinician rating of global improvement. The most informative RCT study was that of Findling et al. [35], which lasted up to 5 years and reported that DVPX in 29 individuals did not prove superior to the 27 on PBO. This study thus coincides with other data in children with BP I mania about the ambiguity of the efficacy of DVPX in children, as opposed to the well-demonstrated efficacy in adults with BP I mania. The third RCT (Findling et al. [34]) compared 30 children randomized to aripiprazole (APZ) for 12 weeks to 29 on PBO in those at high genetic risk for BD and found that APZ decreased mania scores on the YMRS more rapidly than on PBO. These data are of interest to the findings on APZ in BP I adults, where there are positive data for the prevention of total and manic episodes, but not depressions, such that the efficacy on depressive symptoms in Findling et al. [34] remains obscure.

Results with an open-label study of paliperidone for 8 weeks also yielded significant reductions in YMRS scores, as well as improvements in the severity of ADHD and psychotic symptoms. However, increases in body weight over the 8 weeks were substantial. Likewise, in another open study, Joshi et al. [37] found that quetiapine monotherapy for 8 weeks was beneficial in BP spectrum disorder in children aged 4–6 years and 6–15 years, but with very substantial weight gain. These data contrast with the lack of efficacy of quetiapine in an RCT of youngsters with BP depression, as opposed to clear-cut efficacy in adults with BP depression. The open chart review data on quetiapine in 22 youngsters also reported positive effects over 6 months, but only 6 had a USBD diagnosis.

If one takes these open data on atypicals with those of Geller et al. [29], which involved an open randomization to risperidone, lithium, or VPA, it would appear possible that the atypical antipsychotics as a group may have effectiveness in youngsters with early BP spectrum symptoms, but at the cost of substantial weight gain. Moreover, a lack of methodological rigor is inherent in all the case series discussed, including the two longitudinal studies of lithium (Geller et al. [43]; Hafeman et al. [27]), as well as the open case series of Papolos et al. [26] and Papolos et al. [25]. These studies also included the risk of bias, and there was an obvious absence of blinding. In the open randomized studies of Geller without a PBO, there was also a high risk of lack of blinding because of the three active drugs' highly differential side effects.

Again, the Geller et al. [43] data were not presented in such a way as to discern the relative effectiveness in those with USBD compared to those meeting criteria for BP I and BP II. This designation of the "Results Not Given Separately" (RNGS) by diagnosis was the case for most of the open and comparative studies.

However, this was not an issue in the open case series of Papolos et al. [26], where the focus was exclusively on the USBD subtype of TSDD as described below. In addition, the open studies

TABLE 1 | Psychopharmacological studies.

Psychopharmacological studies								
Reference	**Study type**	**Rx**	**Sample**	**Age**	**Clinical features**		**Duration**	**Results**
McNamara et al. [33]	RCT	Fish oil (2100 mg/day) vs. placebo fish oil $N=21$, placebo $N=21$	$N=42$	14.1 ± 3.0 years	High risk with MDD or depressive disorder-NOS, and biological parent with BD-I	RNGS	12 weeks	Fish oil monotherapy was not superior to placebo for reducing depressive symptoms in high-risk youth as assessed by the CDRS-R, but was safe and well tolerated and superior to placebo on clinician ratings of global symptom improvement.
Findling et al. [34]	RCT	Aripiprazole (APZ) vs. placebo	APZ = 30, placebo = 29	5 to 17	High genetic risk with dysfunctional mood episodes	RNGS	12 weeks	YMRS total score decreased significantly more rapidly for APZ than placebo.
Findling et al. [35]	RCT	Divalproex (DVPX) monotherapy	$N=29$ DVPX, $N=27$ placebo	5 to 17	BP-NOS or CYC plus one biological parent with BP	BP-NOS $n=56$	Up to 5 years	Maintenance treatment with divalproex was not significantly different from treatment with placebo.
Joshi et al. [36]	Open-label	Evaluate the safety and efficacy of (RX): paliperidone monotherapy as an acute treatment of mania and related symptoms	$N=15$. Youth with bipolar spectrum disorders	YMRS at entry: 32.8 ± 6.1 were enrolled in the study	Pediatric bipolar spectrum and related disorders (depression, psychosis, attention-deficit/hyperactivity disorder [ADHD])	RNGS	8 weeks	Statistically significant levels of improvement in mean YMRS scores (-18.7 ± 13.9, $p<0.001$) at endpoint. Significant improvement in the severity of ADHD and psychotic symptoms. Increases in body weight (4.1 ± 5.5 lbs) were substantial.

(Continues)

TABLE 1 | (Continued)

Psychopharmacological studies								
Reference	**Study type**	**Rx**	**Sample**	**Age**	**Clinical features**		**Duration**	**Results**
Joshi et al. [37]	Open-label trials (2 sample groups w. identical methodology)	Quetiapine was titrated to a mean endpoint dose of 175.8 ± 63.8 mg/day in preschool and 248.7 ± 153.1 mg/day in school age children	$N = 49$ (30 preschool and 19 school age), 34 (20 preschool/14 school age) completed the trial	Study #1 age 4–6 years, Study #2 6–15 years	Bipolar spectrum disorder	RNGS	8 weeks	Quetiapine monotherapy in preschool and school age children was beneficial for the treatment of BSD. Associated with significant weight gain (+3.1 ± 1.8 and +7.4 ± 7.7 lb. respectively, $p < 0.001$).
Joshi et al. [38]	Open-label	Extended-release carbamazepine monotherapy (788 ± 252 mg/day). Stimulants were allowed during the study	$N = 27$	9.1 years of age	BD-1 ($n = 22$), BD II ($n = 3$), BD-NOS ($n = 2$). At the time of participation, ($n = 18$) were experiencing mixed episodes ($n = 6$) were in manic episodes, and ($n = 3$) were in hypomanic episodes	BP-NOS $N = 2$ RNGS	8 weeks	Moderate antimanic response to CBZ-ER. Overall antimanic response, less robust than some atypical antipsychotics.
Clayton et al. [39]	Open-label	LCn-3PUFA supplementation in the treatment of mania and depression as an adjunct to standard pharmacological treatment	$N = 18$	$F = 16.1 \pm 0.81$ years, M = 13.0 ± 1.06 years	BD I ($n = 7$), BD II ($n = 6$), or BP-NOS ($n = 5$)	BP-NOS $N = 5$ RNGS	6 weeks	Clinician ratings of mania and depression were significantly lower and global functioning significantly higher following supplementation.
Papolos et al. [26]	Chart review	Mean intranasal ketamine[a] dosage = 165 ± 75 mg (range 20–360 mg) administered once every 2–5 (mean 3.0 ± 0.6) days	$N = 12$	15 ± 6.7 years	Treatment refractory BP-NOS with UURC	BP-NOS $N = 12$	1.71 ± 1.36 years.	Highly effective, well-tolerated treatment.

(Continues)

TABLE 1 | (Continued)

Psychopharmacological studies

Reference	Study type	Rx	Sample	Age	Clinical features		Duration	Results
Papolos et al. [25]	Chart review	Ketamine[a] mean dosage (current or at time of discontinuation) was 165 ± 75 mg (range 20–360 mg) administered once every 2–5 (mean 3.0 ± 0.6) days	*N* = 45	15 ± 6.7 years	Treatment refractory BP-NOS with UURC	BP-NOS *N* = 45	6 month–6 years	Mean mprovement on the CGIi was 1.9 ± 0.9. 8 patients were seen as very much improved by both raters, 26 were much improved and only 5 patients were mildly improved or unchanged.
Ghaemi et al. [40]	Chart review	Adjunctive zonisamide mean dose 130 mg/day mean duration 27.0 ± 32.3 weeks	*N* = 35	29.2 ± 12.7 years	BP II = 6 BP-NOS = 14 taking concurrent mood stabilizer	BP-NOS = 14 RNGS	27.0 ± 32.3 weeks	Only 9 patients were moderately to markedly improved, the rest were slightly improved, unchanged or worse.
Soutullo et al. [41]	Chart review	Lamotrigine 100 ± 87.5 mg/day (1.67 ± 1.39 mg/kg/day)	*N* = 5	Mean age = 15.5 ± 1.8 years; range = 14–17	BP I-1, BP II-1, BP-NOS-3	BP-NOS = 3	28 ± 28 weeks	3 BP-NOS very much or much improved. Marked or moderate improvement in 4 patients, 1 patient minimal improvement.
Marchand et al. [42]	Chart review	Quetiapine adjunctive and monotherapy treated (mean duration, 6.1 ± 5.9 months) openly with quetiapine (mean dose, 397.4 ± 221.4 mg/day). Fourteen patients (43.8%) received only quetiapine	*N* = 32	10.8 ± 3.9 years	BP I (*n* = 16), BP II (*n* = 10), cyclothymia (*n* = 2), and BP-NOS (*n* = 4)	BP-NOS *n* = 6 RNGS	6.1 ± 5.9 months	CGI-improvement (CGI-I) score of ≤ 2 at end point was 80.0% for the entire group and 78.6% for the subgroup who received quetiapine monotherapy.

Abbreviations: RNGS, results not given separately by Dx; UURC, ultrarapid or ultradian cycling.
[a]Ketamine was given after lithium, clonidine, and other heat-dissipating strategies.

of Clayton et al. [39] showing improvement with LCn-3PUFA for 6 weeks are difficult to interpret because only four patients had USBD. The chart review of Ghaemi et al. on zonisamide showed it was not effective. The study of Soutullo et al. [41] of lamotrigine ($N = 5$) was too small to be interpreted.

Given the paucity of data on pharmacological treatment effectiveness in the USBD subtypes, the authors focused on the larger open series of Papolos et al. in TSDD, as discussed below.

2.6 | Psychotherapy Interventions in Study Populations That Included Children With BP-NOS

Table 2 includes the psychotherapeutic studies meeting our literature search criteria for the group of children characterized under the rubric of BP-NOS or USBD and other aspects of the BP spectrum including cyclothymia. The control group was most often treatment as usual (TAU) and rarely included a formal PBO arm.

Of the 11 psychotherapy studies included in this review, 9 were RCTs (where the comparator was TAU) and 2 were open-label, 9 were family-focused, primarily cognitive/behavioral or family psychoeducational. The large majority were adjunctive studies administered in conjunction with maintenance medications (MMs). Diagnostic descriptions included well defined categories of BD, while others involved high-risk individuals with positive family histories of BD in first-degree relatives. Similar to pharmacotherapy studies, none of the psychotherapy studies reported results separately distinguishing between distinct diagnostic categories of BPD. However, in contradistinction to pharmacotherapy studies, almost all showed medium to large effect sizes for the broad BP spectrum.

Of note, were three large-scale, family-focused studies of long duration conducted by Miklowitz [53] and Miklowitz et al. [45, 52], which examined the moderating effects of family-focused/psychoeducational interventions, and more specifically, expressed emotion (EE) versus enhanced care, on symptomatic outcomes. These were associated with more rapid recovery from mood symptoms, more time in remission, and a more favorable trajectory of hypomania symptoms compared with brief family education.

Several RCTs have investigated the efficacy of psychotherapy interventions for youths with BD, including BD-NOS and cyclothymic disorder. These studies primarily examine cognitive-behavioral therapy (CBT), family-focused therapy (FFT), dialectical behavior therapy (DBT), psychoeducation, and omega-3 supplementation as adjunctive treatments to pharmacotherapy.

Several studies have assessed the impact of FFT on BP youth. Miklowitz [53] and Miklowitz et al. [51, 52] investigated FFT-A (for adolescents) and FFT-HR (for high-risk youth) and found that FFT accelerated recovery from depressive symptoms but did not significantly delay the recurrence of manic episodes. Notably, the impact of FFT was moderated by parental EE, with youth in high-EE families experiencing greater reductions in both depressive and manic symptoms. Weintraub et al. [46] further explored whether improvements in psychosocial functioning mediated mood improvements in FFT and found that enhanced family functioning contributed to reductions in depressive symptoms, particularly for youth with comorbid anxiety and externalizing disorders. These studies highlight the importance of targeting family dynamics in psychosocial interventions for BP youth, as higher family conflict may exacerbate mood symptoms.

Of the two cognitive behavioral studies, Arman et al. [47] compared an experimental group that combined CBT (C-CBT) and MMs versus MM alone, and found a decrease in depression scores but no effect on manic symptoms or relapse rate. In a trial of DBT versus family skills training (FST) over 1 year, consisting of 18 weeks of either individual DBT or FST, Goldstein et al. [49] found a large effect size for more weeks being euthymic among adolescents receiving DBT and significantly greater attendance at therapy sessions than those receiving psychosocial treatment alone.

Goldstein et al. [49] conducted a pilot RCT comparing DBT to TAU in adolescents aged 12–18 years with BD. DBT resulted in greater therapy engagement, fewer depressive symptoms, and lower suicidal ideation compared to TAU. Although no significant differences were observed in manic symptoms, adolescents in the DBT group demonstrated improvements in emotional dysregulation and had more weeks of euthymia over the follow-up period. This suggests that DBT may be particularly useful for mood stabilization and suicidality in this population.

Finally, Fristad et al. [48] examined the efficacy of Individual Family Psychoeducational Psychotherapy (IF-PEP) and omega-3 fatty acid supplementation in youth with BD-NOS and cyclothymic disorder. IF-PEP was associated with moderate-to-large reductions in depressive symptoms, while omega-3 supplementation had a smaller effect. These results indicate that psychoeducation can be an effective intervention for managing mood symptoms, and while omega-3 supplementation may provide mild benefits, it is not sufficient as a standalone treatment.

Overall, these studies suggest that psychosocial interventions, particularly those incorporating family involvement, can be beneficial for BP youth, especially in reducing depressive symptoms. While FFT, psychoeducation, and CBT-based approaches show promise in improving mood stability and psychosocial functioning, their effects on manic symptoms remain inconclusive. Additionally, parental EE appears to moderate treatment outcomes, emphasizing the need to consider family dynamics when implementing psychotherapy interventions for youth with BD.

2.7 | Discussion

This review focuses on two different definitions and subtypes of what is now called USBD. The first is the more readily observed that was initially called BP-NOS because of its attenuated durations of mania. Its recognition and definition have migrated over time and are now subsumed under the rubric of S-USBD,

TABLE 2 | Psychotherapeutic studies.

Psychotherapy studies

References	Study type	Rx	Sample	Age	Clinical features	BP type	Duration	Results
Backstrom et al. [44]	Open		$N=45$ adolescents, $N=61$ parents	13–18 years	BP I $N=15$ BP II $N=14$ BP-NOS $N=13$	BP-NOS $N=13$ RNGS	6 months	Most results after treatment showed medium effect sizes. Psychosocial function, as rated by parents and clinicians, reported less mania and improved family climate at post-treatment. Both parents and adolescents reported improved skills and knowledge.
Miklowitz [45]	RCT	Family-focused therapy for youth at high risk (FFT-HR) vs. enhanced care	$N=127$	13.2 ± 2.6	High risk with MDD or other specified bipolar, family hx BD	RNGS	98 weeks	Longer interval prior to the new mood episode. Lower level of suicidal ideation.
Weintraub et al. [46]	RCT	FFT compared to psychoeducational-only randomized to either 4 months of FFT or EC	$N=119$	Aged 9.0–17.11	Active mood symptoms and a family history of BD	RNGS	2 years	Youths in FFT reported greater improvements in family functioning over 24 months compared to those in EC, $F(5, 76.8)=3.1$, $p<0.05$. The effects of FFT vs. ED on family functioning were stronger among youth with comorbid anxiety and externalizing disorders than among youth without these comorbid disorders.
Arman et al. [47]	RCT	Maintenance medications (UMM) and group cognitive-behavioral therapy (G-CBT)	$N=32$	12–19 years	GCBT and maintenance medications	RNGS	6 months	G-CBT plus UMM leads to a decrease in the depressive scores but has no effect on manic symptoms and relapse rate.

(Continues)

TABLE 2 | (Continued)

Psychotherapy studies								
References	**Study type**	**Rx**	**Sample**	**Age**	**Clinical features**	**BP type**	**Duration**	**Results**
Fristad et al. [48]	RCT (4 groups)	Omega-3; active monitoring (AM), placebo (PBO), individual-family psychoeducational psychotherapy (IF-PEP), and their combination	$N = 23$	14.2 ± 2.2 years	BP-NOS or cyclothymia	RNGS	12 weeks	Effect of IF-PEP on child depression compared with AM was medium ($d = 0.63$, CDRS-R) to large ($d = 1.24$, KDRS). Effect of omega-3 on depression was medium ($d = 0.48$, KDRS).
Goldstein et al. [49]	RCT	Trial of dialectical behavior therapy (DBT) vs. family skills training (FST)	$N = 14$ DBT $N = 6$ psychosocial treatment	12–18	BP I $n = 3$, BP II $n = 5$, BP-NOS $n = 6$	BP-NOS $N = 6$	1 year consisting of 18 weeks or individual of DBT vs. FST	A large effect size for more weeks being euthymic among adolescent DBT. Adolescents receiving DBT attended significantly more therapy sessions than those receiving psychosocial treatment.
West et al. [50]	RCT	Child- and family-focused cognitive-behavioral therapy (CFF-CBT) for BP vs. psychotherapy as usual	$N = 69$	9.19 years, SD = 1.61	BP I, BP II, and BP-NOS	RNGS	12 weekly sessions, followed by 6 monthly booster sessions delivered over 9 months	CFF-CBT demonstrated efficacy compared to the control treatment in reducing parent-reported mania at posttreatment and depression symptoms at posttreatment.
Miklowitz et al. [51]	RCT	Family-focused therapy (FFT)	$N = 40$ M/23 F/17	12.3 ± 2.3 years	High-risk youths with active symptoms of MDD or unspecified (subthreshold) BD and a first-degree relative with BD I or BD II	RNGS	12.3 ± 2.8	FFT is associated with more rapid recovery from mood symptoms, more time in remission, and a more favorable trajectory of hypomania symptoms compared with brief family education.

(Continues)

TABLE 2 | (Continued)

Psychotherapy studies

References	Study type	Rx	Sample	Age	Clinical features	BP type	Duration	Results
Miklowitz et al. [52]	RCT	Studied the moderating effects of parental expressed emotion (EE) on 2-year symptomatic outcomes	$N = 58$	12.0–17.11 years	BP I ($n = 38$), BP II ($n = 6$), or NOS ($n = 14$)	BP-NOS $N = 14$ RNGS	2 years (1 year treatment, 1 year follow-up)	Adolescents in high EE families showed more dramatic responses in 21 session FFTA than to 3 sessions EC in terms of improvement of depressive and manic symptoms.
Miklowitz [53]	RCT	Family-focused therapy vs. enhanced care pharm	$N = 58$	12.0–17.11 years	BP I ($n = 38$), BP II ($n = 6$), or NOS ($n = 14$)	BP-NOS $N = 14$ RNGS	2 years (1 year treatment, 1 year follow-up)	Patients in FFT-A spent less time in the acute phase of depression than the EC group and spent more time without symptoms of depression.
West et al. [54]	Open-label	Child and family-focused cognitive behavioral therapy	$N = 26$	6–12 years	Forty-six percent of children had a primary diagnosis of BP-NOS; 39% BP I; and 4% with BP II. 54% of participants had comorbid ADHD; 8% a comorbid anxiety disorder; and 4% comorbid Asperger's disorder.	BP-NOS $N = 12$ RNGS	Not provided	Significant improvement in manic, but not depressive, symptoms and in children's psychosocial functioning post-treatment.

Abbreviation: RNGS, results not given separately by Dx.

but it is clearly prevalent and one of the earliest presentations of childhood BD. Childhood-onset BD was recognized as early as Kraepelin [55], but modern psychiatry imbued its presence with controversy and disagreements about its definition, as discussed above.

BP I and II are now well recognized in clinical and epidemiological samples, although the average age of onset appears to differ in many locales [7–9]. BP-NOS was precisely described and defined by Birmaher et al. [1] in their COBY studies and seen as a very early and severe subtype which, upon several years of follow-up, often (about 50% of the time when there was a positive family history of BD) evolved into more classical presentations of BP I and BP II.

Disappointingly, treatment studies of BP-NOS were rarely undertaken as separate studies in this discrete population, and most of the information about treatment was indirectly inferred from the few studies on BP I children [2] and in a few studies that included this BP-NOS subtype within the larger study cohort [1, 27, 29]. Lithium appears to be an increasingly appreciated approach to those with childhood onsets with a range of BP spectrum diagnoses. Risperidone, in a randomized, open study, proved more effective than lithium or valproate but was limited by increased side effects [29]. Other better-tolerated atypicals have not been studied in USBP, although lurasidone is FDA-approved for children 10–17 with BP depression [56]. It and other well-tolerated atypicals deserve specific study in this first subtype of the USBD population. Thus, it is important to note that even in the most common and well-recognized form of what was originally called BP-NOS, several initial pharmacological approaches have received some support, but treatment sequences following these to achieve good long-term outcomes are obscure and remain to be defined. There is currently no consensus among experts in child and adult BD as to how to proceed [57].

This review highlights a second subtype of USBD, that of TSDD, which has all the elements of BP-NOS, but also some unique features not present in the traditional description of BP-NOS by Birmaher et al. [1]. The three major clinical characteristics that differentiate TSDD from classic BP-NOS include (I) fear-based aggression with suicidal and homicidal ideas and actions; (II) thermal dysregulation with overheating seen with the presence of a flushed face and red ears and a high tolerance for cold; and (III) marked sleep disturbance with multiple arousals, horrific nightmares, and terrors.

If these three differentiating elements are recognized and addressed, these extremely dysregulated and impaired children can be treated with a regimen pioneered by Papolos et al. [25]. It involves high-dose lithium, clonidine, melatonin (*N*-acetyl-5-methoxy tryptamine), and other measures to enhance body cooling, sleep onset, and parasomnias; and then ascending doses of intranasal ketamine to find an optimal maintenance dose. We emphasize that these clinical case series observations have not yet been supported by evidence from controlled clinical trials. However, this unusual combination of treatments deserves presentation and discussion, as the conventional treatments typically employed in these children are usually ineffective. This leaves children with TSDD and their families highly dysfunctional, and social and educational opportunities become limited throughout their adolescence and early adulthood.

2.8 | TSDD, Formerly Termed FOH, Is a Unique Subtype of USBD

Besides the children described as BP-NOS by Birmaher et al. [1], who exhibit all the classical features of BD except for the duration of mania, there is a second subgroup of children that meet criteria for USBD that deserves special attention. These children, now classified as TSDD, were initially labeled with the diagnosis of FOH phenotype described in detail by Papolos and colleagues [58, 25–60, 61–26]. FOH was based on a dimensional diagnosis derived from a concordance study between affected sibling pairs that found a heritable behavioral trait associated with a profile of clinical dimensions in addition to classic mood symptomatology, delineated from a database of 6500 symptom profiles from children with or at risk for BD. These children with TSDD also met all the Birmaher et al. [1] (Birmaher and Axelson [31]) criteria for BP-NOS, but they also have three other unique characteristics. These include:

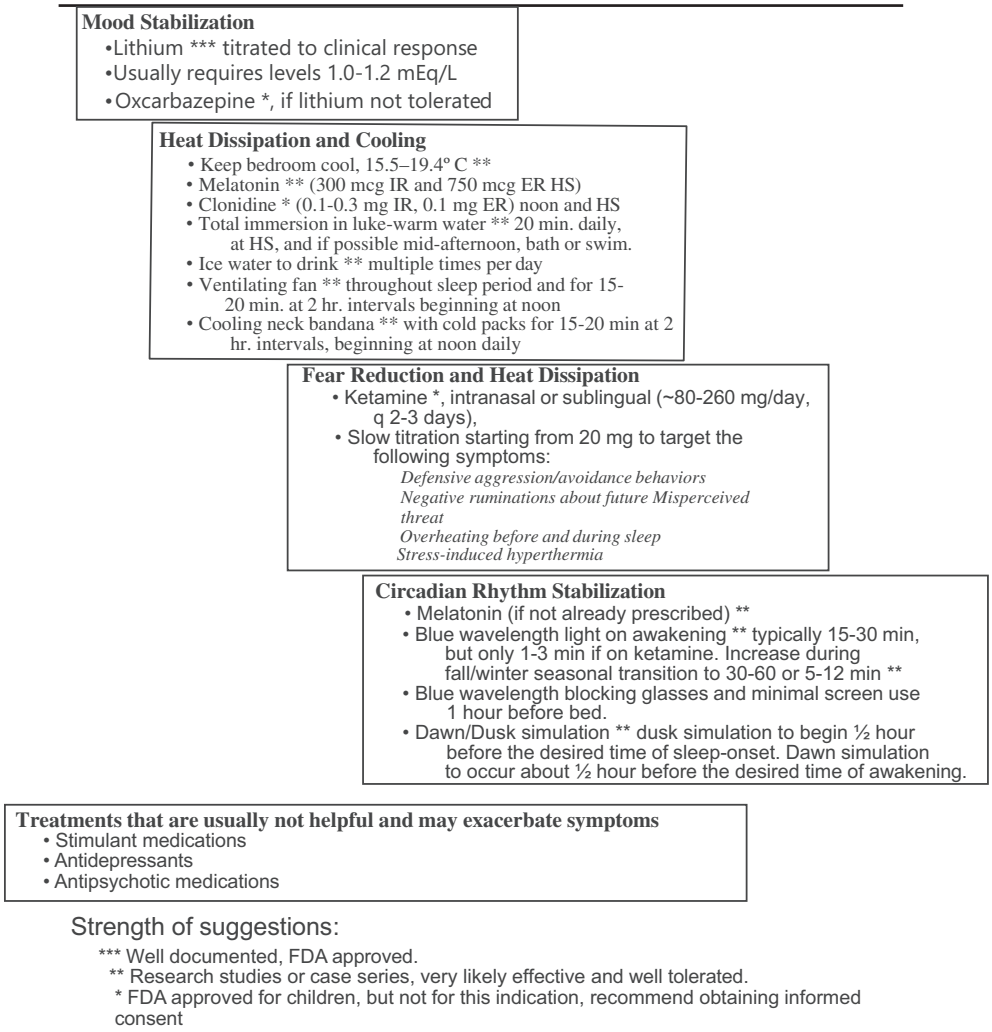
I. *FOH*: FOH to self and FOH to others, defensive aggression directed toward others and self, separation anxiety, aggressive obsessions (including recurrent self-recriminatory thoughts), misperception of neutral stimuli as threatening, and behavioral symptoms that mimic those of post-traumatic stress disorder (PTSD), along with abrupt, rapid transitions of mood and arousal.

II. *Thermal dysregulation*: Children with TSDD often feel hot and sweat excessively in neutral ambient temperatures and in response to emotional stimuli (stress-induced hyperthermia). This overheating is evident by the flushed appearance of the cheeks and the bright red color of the pinna of the ears. TSDD children are also often tolerant of or insensitive to cold temperatures and will comfortably venture out with little clothing on cold winter days. They alternate noticeably between being excessively hot in the evening and cold in the morning. This tendency to generate excessive heat or a deficit in heat dissipation at night results in shortened REM latency and disturbances in REM/NREM transitions during sleep in childhood and beyond [58] (Papolos, unpublished observations).

III. *Sleep disturbances*: These include sleep-onset insomnia and morning sleep inertia, as well as parasomnias (night terrors, horrific and vivid nightmares, sleep-walking, sleep-talking, bruxism, enuresis, and sleep–wake reversals).

Given the lack of clear guidelines for the treatment of the well-recognized BP-NOS subtype of USBD, but new information about a highly effective treatment regimen for the TSDD subtype of USBD, we highlight the specific characteristics that distinguish TSDD from BP-NOS. If clinicians explicitly ask about these unique elements, they will likely recognize some children with TSDD. We summarize in Table 3 some of the key aspects of the syndrome that should raise a clinician's suspicion that they reflect the TSDD syndrome and not the more traditional

TABLE 3 | A preliminary treatment paradigm for the S-USBP subtype of TSDD.



aspects of BP spectrum disorder and its many well-recognized comorbidities.

I. *FOH*
   A. Fear of the dark, fear of intruders, and separation anxiety
   B. Defensive aggression toward others
   C. Self-directed aggressive behavior (bites, hits, and cuts self)
   D. Misperceives neutral stimuli as threatening
   E. Concern about dirt, germs, and contamination

II. *Temperature dysregulation*
   A. Pinna of ears bright red (during periods of anxiety, anger, or embarrassment)
   B. Facial flushing (during periods of anxiety, anger, or embarrassment)
   C. Excessive sweating (during exercise, before and during sleep, in response to perceived threat)
   D. Moderate to extreme tolerance to cold (goes out underdressed and without a coat in cold ambient temperatures)
   E. Sensitive to seasonal and rapid changes in temperature, humidity

III. *Distinctive sleep disturbances*
   A. Nightmares (with gore, blood, and violence)
   B. Night terrors (child wakes up screaming)
   C. Hypnagogic hallucinations (of threatening individuals)
   D. Sleep-walking and sleep-talking
   E. Sleep inertia
   F. Sleep phase delay disorder
   G. Enuresis
   H. Bruxism

IV. *Other aspects (but not a separate subtype)*
   A. Carbohydrate craving and binging
   B. Hoards or avidly seeks to collect objects or food

TSDD is associated in early childhood with the advent of recurrent, vivid, gory, horrific nightmares with themes of pursuit and abandonment. The apparent psychological sequelae of exposure to this frequent, frightening imagery is fear sensitization (autotraumatization). A developmental sequence of fear-based defensive behaviors results, including obsessive/anxious bedtime rituals, fear of the dark, separation anxiety, intruder and contamination phobias, hypervigilance, misperception of neutral stimuli as threatening, and reactive aggression in response to limit-setting

and perceived threat or loss. In parallel, an ensemble of fear-based cognition and behaviors evolves into adulthood patterns that become prominent traits and dominant personality features. This sequence can be interrupted or modified appreciably with early identification and intervention as described below [61, 63].

The core features of FOH/TSDD emerged from an effort to identify homogeneous phenotypes for genetic studies of pediatric BD using an endophenotype approach similar to Cheng et al. [64] and Faraone et al. [65] in a large sample of youths ($N = 5335$) who had been given a community diagnosis of BD or were at high risk to develop this disorder based on an enriched family history [60, 61]. Of the 10 factors extracted from the Child Bipolar Questionnaire (CBQ), the strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between proband/sibling versus proband/comparison pairs, were for the factor termed FOH, which strongly suggests that it is a heritable trait [60].

2.9 | A Preliminary Treatment Paradigm for TSDD

The general treatment strategy outlined here has been described by Papolos et al. [25, 26] and is associated with marked improvement in behavior, sleep, and physiological dysfunction. The essence of the treatment paradigm is outlined in Tab. 5. The details of the treatment protocol are further delineated in a supplement available at https://www.jbrf.org/treatment-protocol/. A few of the significant components of each of the suggested treatments are reviewed below.

2.9.1 | Lithium

In adult studies, lithium has the most substantial evidence for long-term relapse prevention; the evidence for anticonvulsants such as divalproex and lamotrigine is less robust, and there is much uncertainty about the longer-term benefits of antipsychotics [66]. Lithium is clinically effective in roughly half of the treated individuals, where their genetic background is known to influence treatment outcomes [67].

As described above for children with both BP-NOS and BP I, lithium has an increasingly recognized role in the treatment of childhood-onset BD [27, 29, 68, 69]. In the clinical sample with TSDD of Papolos et al. [25], higher serum lithium levels within the upper range of normal (1.0–1.2 meq/L) were often necessary to achieve complete mood stabilization. Additionally, lithium is neuroprotective and has many other assets beyond mood stabilization [70], and has also been found to specifically protect against high-dose ketamine-induced apoptosis in primate toxicology studies [71].

2.9.2 | Oxcarbazepine

One of the most important advances in psychopharmacology of the last century was the recognition of the mood-stabilizing properties of lithium [72, 73]. This was followed years later by the recognition that carbamazepine and other anticonvulsants have mood-stabilizing properties as well [74]. Clinical experience favors lithium for treating TSDD, but oxcarbazepine (OXC) extended release (Oxtellar XR) may be a satisfactory adjunct or alternative if lithium cannot be tolerated. In a randomized study cited as a negative, OXC was more effective than PBO in the subgroup of younger patients aged 7–12 years of age, but not adolescents 13–17 [75]. In a large open retrospective case series, OXC was highly effective across a diverse array of childhood psychiatric symptoms [76]. OXC is usually given twice a day, but the long-acting preparation Oxtellar can be conveniently given in a single night-time dose. OXC should be titrated slowly to avoid side effects, but doses can range from 600 to 1500 mg HS.

2.9.3 | Sleep and Bedroom Temperature

Room temperature is a critical determinant of sleep quality, especially for youths with TSDD. Sleep experts suggest an optimal room temperature range of 15.5°C–19.4°C for children, adolescents, and adults, and only slightly higher for infants and toddlers [77]. Nocturnal heat dissipation is critical for sleep initiation and REM stability [78, 79].

2.9.4 | Melatonin

Melatonin, an evolutionarily ancient peptide derivative of tryptophan with hormonal properties, is synthesized by the pineal gland in most vertebrate species and is directly released at night into the blood. In all species, including ancient bacteria, it serves an essential role as an antioxidant. In present-day animals, melatonin functions in regulating sleep, modulation of circadian rhythms, and enhancement of immunity [80, 81].

Melatonin plays a vital role in sleep induction via its effects on vascular tone. Briefly, sleep onset is coupled to the shifting of circulation from the core to the periphery, which increases skin temperature, enhances heat dissipation, and lowers core body temperature. Melatonin serves as nature's nocturnal vascular modulator by regulating vascular tone in selective vascular beds as circulating melatonin levels rise and fall throughout the night [82].

Abnormal melatonin circadian rhythms are a hallmark of sleep disorders, characterized by a misalignment between the sleep period and the physical/social 24-h environmental cycle. Exogenous melatonin can stabilize these periodic disruptions in sleep and activity rhythms [83, 84]. Patients with mood disorders and TSDD have repeatedly been shown to have irregular circadian rhythms compared to healthy control subjects [58, 80, 85–87]. Several studies have observed that patients with mood disorders have abnormal melatonin secretion, including a later nocturnal peak secretion, reduced secretion amplitude, and a super-sensitive suppression of melatonin secretion by light [86]. Melatonin (usually 0.5–5 mg daily, although doses lower than 3 mg are often sufficient) can synchronize a non-24 h sleep–wake cycle to 24 h in the vast majority of patients [83, 88, 89]. In TSDD, closer to physiological doses of melatonin, 600 mcg immediate release (IR) and 750 mcg extended-release (ER) an hour before sleep, can be utilized.

2.9.5 | Clonidine

Clonidine, a selective, partial [alpha]$_2$-adrenoreceptor agonist that acts centrally and peripherally as a vasodilator, has significant effects on thermoregulation [90–93]. The long-acting formulation is approved for use in the treatment of attention deficit/hyperactivity disorder and has long been used off-label to treat stimulant-induced insomnia [94, 95]. In individuals with TSDD, clonidine has been used primarily to promote heat dissipation, improve sleep initiation (reduce early insomnia), and enhance sleep continuity.

Emotionally significant stimuli, including potential threats from the external environment, can trigger an increase in body temperature, a response known as emotional hyperthermia [96]. Clonidine ER inhibits sympathetically mediated brown adipose tissue thermogenesis, which contributes substantially to this hyperthermic response, and clonidine has been used effectively to improve heat dissipation and inhibit heat generation [92, 97–99], and appears to function in this manner in TSDD (Papolos, unpublished observations). Clonidine is started at 0.1 mg IR HS and slowly titrated to 0.4 mg IR. If overheating and stress-induced hyperthermia are present, it can be given in the mid to late afternoon in IR or ER forms, weighing benefits against sedation. Periods of stress-induced hyperthermia accompanied by irritable/elated mood states, hyperactivity, and aggressive/explosive outbursts often occur diurnally in the mid to late afternoon.

2.9.6 | Thermal Cooling

Adjunctive measures to enhance body cooling through an increase in heat dissipation include total body immersion (bath or pool in lukewarm water), ventilation (mobile and oscillating fans worn around the neck or rotating in place near open areas of skin), and direct cooling (ice bandanas, ice hats that directly cool neck and scalp veins), as well as ambient temperature and humidity adjustments. These methods are implemented before or at the time of the initiation of pharmacological treatment [25, 26]. Several basic principles and assumptions guide the typical cooling schedule: (1) on arising from a supine position from sleep, heat is generated through muscular movement and brain activity; (2) when supine at the time of sleep onset, vasodilation enhances the release of heat as insensible loss as the body cools; (3) individuals with TSDD have a disturbance in the capacity to transfer heat from the core to the periphery. They sequester heat within the body over the day, have an excessive hyperthermic response to stressors (emotional hyperthermia), and overheat when supine before sleep onset.

Total body immersion in warm water for 15–20 min and an oscillating cooling fan at the bedside are helpful and convenient strategies. When feasible, a typical daily thermal cooling routine begins every 2 h from 12 noon to 6 pm and thereafter. At these times, the youngster drinks 12–16 oz. of ice water to cool the core and ventilates the face with a fan for 15 min. Alternatively, an ice hat or cooling neck bandana is used. (Note: Children taking lithium need to maintain stable sodium levels, which can be facilitated by drinking isotonic solutions such as Propel or Gatorade-Zero.)

2.9.7 | Ketamine

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist known foremost for its anesthetic, analgesic, and antishivering properties, is a racemic mixture comprised of equal parts of (*R*)-ketamine and (*S*)-ketamine [100]. It did not have a clinical indication in psychiatry until March 2019 with the FDA approval of intranasal Spravato [(*S*)-ketamine] for refractory depression (2019) [101].

Ketamine was initially selected as a potential treatment for TSDD when it became apparent that mood stabilization alone with lithium was insufficient to abolish the cardinal symptoms of the syndrome. A literature review at the time (circa 2006) revealed that ketamine was the only drug found in animal studies to dramatically reduce conditioned fear and fear sensitization and dose-dependently decrease core body temperature. It was in widespread use, could be safely administered to children, and was approved by the FDA for other indications [102–104].

Though RCTs have not been conducted, clinical experience and naturalistic studies with retrospective blind chart reviews have found that individuals with TSDD typically have a good to excellent response to intranasal ketamine, which appears to work optimally when combined with lithium, with enduring benefits for as long as the patients have been followed with regular intermittent intranasal ketamine treatment [25]. Rarely have adverse effects required ketamine discontinuation. There has been no evidence of abuse of the drug in over 200 cases followed clinically by Papolos et al. [26].

The first known administration of racemic ketamine in TSDD was given as a 0.3 mg/kg slow iv infusion to a 4½-year-old child during a dental procedure. Within 2 h following the procedure, parents observed that most, if not all, of the defining symptoms of TSDD ceased, including separation anxiety, fearfulness, agitation, oppositional/aggressive behaviors, debilitating recurrent nightmares, as well as the thermal dysregulation that had characterized her presentation prior to the infusion. She remained asymptomatic for 10 days, but then thermal discomfort (overheating, facial flushing, reddened ear pinnae followed by sleep-onset insomnia and nightmares) reappeared. This patient has remained stable on lithium salts (serum level 1.1 mM) and three times weekly instillations of intranasal ketamine for a decade and has recently matriculated to college.

Papolos et al. [25] found that a solution for the administration of intranasal racemic ketamine can be compounded effectively at concentrations in the range of 100–150 mg/mL. In its native form, ketamine is a crystalline substance that can more easily precipitate out of solution above 150 mg/mL. The effective shelf life of ketamine kept in darkness at room temperature is probably not more than 4 weeks.

To initiate treatment, a solution of 100 mg/mL is administered into each nostril in a 0.1 mg metered spray bottle (10 mg/spray) that is readily available by physician's prescription at most compounding pharmacies in the United States. Additional insufflations are given incrementally depending on clinical assessment over 25 min until mild ataxia or signs of early dissociative effects appear. An incremental dose titration delivered every other day

is based on signs of clinical improvement and the development of tolerance to acute adverse effects.

Papolos et al. [25] found that the measurement of therapeutic efficacy relied on two primary outcome measures: daily changes in the FOH Index (FOH-I) determined from a parental rating of an eight-item Likert scale and resolution of the majority of core phenotype symptoms on the CBQ [63]. Typically, the thermoregulatory symptoms improve first in tandem with sleep-onset insomnia and sleep continuity.

2.9.8 | Blue Wavelength Light

Patients with TSDD exhibit delayed sleep onset, are typically hot before sleep, and often have night sweats. In TSDD, this form of early insomnia is strongly associated with a disturbance in the distal-minus proximal temperature gradient (DPG^0), a circadian marker for sleep onset in humans [105]. Because these patients have a significant delay in the main sleep period relative to the sleep–wake time, the usual zeitgebers for arousal into social life are lost. This combination of disturbances in sleep and arousal, difficulty falling asleep as well as difficulty waking up, sleep inertia, daytime sleepiness, and poor energy, is a form of circadian sleep disturbance commonly referred to as delayed sleep–wake phase disorder (DSWPD) [106], and officially termed Circadian Rhythm Sleep–Wake Disorder—delayed sleep phase type in DSM-5.

Circadian rhythms are entrained by light, with relatively recent studies showing that intrinsically photosensitive retinal ganglion cells, rather than rods or cones, convey information to the suprachiasmatic nuclei and other non-visual brain regions. These cells use a unique photopigment called melanopsin and are specifically responsive to blue wavelength light at around 460–470 nm [107]. Hence, blue wavelength light is particularly effective in regulating circadian rhythms and may require less time and/or lower light irradiance than full-spectrum or white light [107]. Blue light therapy has been reported to improve subjective sleep quality, reduce the number and duration of nocturnal awakenings, improve daytime function, and phase shift the sleep cycle [106].

In TSDD, we use blue wavelength light (Philips goLITE BLU) as an alerting signal upon awakening to diminish morning sleep inertia and to entrain and phase advance the circadian clock. Typically, this requires 15–30 min of exposure. However, clinical experience has demonstrated that ketamine appears to markedly potentiate the activating effects of blue wavelength light. For example, while 30–45 min of light is typically prescribed to diminish symptoms of seasonal affective disorder during the fall–winter transition, individuals with TSDD receiving ketamine may benefit from only 1–10 min of blue wavelength light. They can experience symptoms of agitation and hypomania with more prolonged exposure periods. Accordingly, a typical titration schedule for youth receiving ketamine begins with 2 min of bright light exposure at 200 lx, which is increased by 1 min each day until the desired clinical outcome is achieved. The usual dosage range is 200 lx for 3–10 min. This device can be beneficial during seasonal transitions when the photoperiod abruptly changes from alternately longer dark to longer light periods.

Interestingly, there are some important similarities between TSDD and PTSD, with patients with TSDD becoming fear-sensitized or auto-traumatized by their nightmares. Recent studies have reported that morning treatment with blue wavelength light diminished sleep complaints and symptom severity and facilitated fear extinction in PTSD [108]. Further, morning treatment with blue wavelength light increased total sleep duration and left amygdala volume, which was associated with a reduction in nightmare severity [109].

Conversely, nocturnal exposure to blue wavelength light from smartphones, laptops, and other devices can significantly delay sleep onset and reduce sleep quality [110]. Hence, we recommend that individuals with TSDD use blue light-blocking glasses and limit their screen time for an hour or more before bedtime.

2.9.9 | Dawn Simulation

Dawn simulation can be used as an alternative to the early morning use of blue wavelength light. A meta-analysis (based on 127 patients in 3 trials) by Golden et al. [111] found that dawn simulation and bright light therapy reduced depressive symptom severity more than PBO for seasonal affective disorder and that bright light therapy also reduced symptom severity [111]. A single dawn signal applied by devices such as the Smart Sleep and Wake-up Light (Philips, Cambridge, MA, USA) can simulate the waveform of the dawn or dusk signal at any latitude and any day of the year and is sufficient to phase advance melatonin secretion and phase shift the circadian pacemaker in primates at a fraction of the white light illuminance previously used after awakening [112]. For patients with TSDD and a delayed sleep phase-type circadian rhythm sleep–wake disorder, it is recommended that dusk simulation begin a ½ hour before the desired time of sleep onset [106] and that dawn simulation should be set to occur about a half hour before the desired time of morning awakening. For this treatment to be effective, dusk and dawn simulation should take place in an otherwise darkened room.

2.10 | What About Second-Generation Antipsychotics?

Hobbs et al. [3] recommended using second-generation antipsychotics (SGAs) as the first step in treating mania and mixed states in youth with BP 1 disorder. Their second recommendation was to try a different SGA if the first was not successful. Most of the youths with TSDD treated successfully using the approach outlined in this article had previously been prescribed an array of SGAs but experienced little, if any, clinical benefit [25, 26]. One possible explanation is that dopamine [113] and serotonin [82] play critically important roles in thermoregulation. Hence, drugs that interfere with dopaminergic or serotonergic neurotransmission can interfere with thermoregulation, and both first- and second-generation antipsychotic medications have been associated with thermoregulatory problems, including hyperthermia, hypothermia, and, in the most extreme cases, neuroleptic malignant syndrome [114, 115]. Hence, it may be the case that SGAs are less effective in individuals with TSDD, as these agents may further compromise their ability to thermoregulate effectively. Of note, lithium monotherapy, which should

I. Fear of Harm

A. Fear of the dark, fear of intruders, separation anxiety
B. Defensive aggression toward others
C. Self-directed aggressive behavior (bites, hits, cuts self)
D. Misperceives neutral stimuli as threatening
E. Concern about dirt, germs, and contamination

II. *Temperature Dysregulation*

A. Pinna of ears bright red (during periods of anxiety, anger, or embarrassment)
B. Facial flushing (during periods of anxiety, anger, or embarrassment)
C. Excessive sweating (during exercise, before and during sleep, in response to perceived threat)
D. Moderate to extreme tolerance to cold (goes out under-dressed and without a coat in cold ambient temperatures)
E. Sensitive to seasonal and rapid changes in temperature, humidity

III. *Distinctive Sleep Disturbances*

A. Nightmares (with gore, blood, and violence)
B. Night terrors (child wakes up screaming)
C. Hypnogogic hallucinations (of threatening individuals)
D. Sleep-walking, sleep-talking
E. Sleep inertia
F. Sleep phase delay disorder
G. Enuresis
H. Bruxism

IV. Other Aspects (but not a separate subtype)

A. Carbohydrate craving and binging
B. Hoards or avidly seeks to collect objects or food

FIGURE 3 | Clinical flags that indicate that a child might have TSDD rather than the typical BP-NOS subtype of USBD.

be helpful in patients with TSDD, was the next recommended approach by Hobbs et al. [3] in their treatment algorithm for patients with BP I if two trials of SGAs were ineffective.

It is important to emphasize that this second TSDD subtype of USBD is not uncommon, but is almost always missed by clinicians. These children have typically previously received one or more of the following diagnoses: attention deficit disorder with hyperactivity; DMDD; separation anxiety disorder; simple phobias; social phobia; generalized anxiety disorder; ODD; nightmare disorder; and obsessive-compulsive disorder. Typically (in order of the frequency of their use), they had been prescribed: stimulants (methylphenidate, dextroamphetamine, dexmethylphenidate); antidepressants (fluoxetine, venlafaxine, bupropion): atypical antipsychotics (e.g., APZ, olanzapine, quetiapine, risperidone, and ziprasidone); anxiolytics (e.g., clonazepam and lorazepam); mood stabilizers (e.g., lithium, lamotrigine, and valproate), all with minimal benefit [25, 61]. TSDD patients were commonly prescribed combinations of psychotropics, most often a stimulant or antidepressant that almost very often worsened the course of illness by increasing cycle frequency or intensifying irritability and aggression, and not infrequently resulted in hospitalization.

In contrast to these more conventional approaches used for those with BP-NOS, Papolos et al. [25, 26] describe a different treatment paradigm for those with TSDD, as outlined in Table 3. It involves lithium for mood stabilization, followed by several approaches to temperature and sleep regulation (including melatonin and clonidine), and then initiation and titration of intranasal ketamine. When this regimen, as augmented by additional cooling measures (such as baths, iced drinks, cold compresses, and ventilating fans) is utilized, severely impaired children can begin to have a good outcome, including the ability to attend regular school, cease fighting with parents, make new friends, and resume a more age-appropriate developmental trajectory [61, p. 61, 26, p. 26] as seen in over 10 years of clinical follow-up observations.

Many unanswered questions remain about the TSDD subtype of USBD. Of particular concern is the absence of any RCTs. How common is it in systematic epidemiological studies? Is the efficacy of the reported positive results with lithium, ketamine, clonidine, melatonin, and other cooling techniques unique to TSDD, or would some patients with a more classical BP-NOS subtype also respond to this paradigm? Does the overt group of physiological clinical signs and associated symptoms suggest that thermoregulation is part of the underlying pathophysiology of the condition [113, p. 117]? Are the effects of ketamine, clonidine, and melatonin related explicitly to direct effects on improving core cooling via heat dissipation, and the question remains as to whether other thermoregulatory manipulations would also be effective? Since the PRS of those with BP-NOS were as high as those with the different subtypes of the BP spectrum [18], it would be of considerable interest to determine whether PRS scores in those with TSDD were similarly elevated. A related question is whether individuals with TSDD share some inflammatory markers (such as CRP) and other biological and brain imaging markers seen in those with BP-NOS and the rest of the BP spectrum [116, p. 119, 117, p. 121, 118, p. 122].

There have been many diagnostic challenges, particularly those related to developmental presentations and the changing progression of symptoms and cyclicity over the life cycle. Of the various USBS subtypes, as exemplified by DMDD, which has been ruled out as a BP subtype, we have focused on two discrete, clearly defined syndromes, BP-NOS and TSDD.

3 | Discussion

We conclude this systematic review with the disappointing observation that optimal pharmacological treatment of the most widely recognized BP-NOS subtype of USBD needs significant further study. In contrast, the literature is quite substantial on the effectiveness of FFT and related family-based psychotherapies [51, 119, 120]. Besides these psychotherapeutic approaches, there is a paucity of data on early pharmacological intervention and prevention [57, 121].

With the recognition that the FOH syndrome, as originally designated by Papolos et al. [61], had the additional elements of prominent thermal dysregulation and marked sleep disturbances that included recurrent, horrific nightmares (as described above and in Figure 3), it may now be more appropriate to refer to this syndrome as TSDD. We highlight this second subgroup of those that meet criteria for USBD in this discussion because the TSDD syndrome needs to be more widely recognized and has an unconventional treatment paradigm not recognized for the typical BP-NOS subgroup.

The less well-recognized TSDD subtype also suffers from a lack of controlled clinical trials, but for these TSDD children, there are robust clinical observations and case series that suggest that very good long-term outcomes are possible. This is achieved when the rapid cycling mood, energy, and arousal disturbances are addressed with lithium, and when fearfulness, temperature, and sleep dysregulation are treated with intranasal ketamine, melatonin, clonidine, and other practical cooling measures. It is hoped that with wider recognition of the occurrence of the several different subtypes of USBD, including both typical BP-NOS and the distinct TSDD, it will lead to more systematic study and the conduct of controlled clinical trials to better define optimal treatment approaches to each of these early presentations of BD.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in Google at https://www.google.com. These data were derived from the following resources available in the public domain: Embase, https://www.elsevier.com/products/embase and PubMed, https://pubmed.ncbi.nlm.nih.gov.

Peer Review

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Supporting Information

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