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REVIEW

Maintenance Pharmacological Treatment of Juvenile Bipolar Disorder: Review and Meta-Analyses

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ABSTRACT

Background: Guidelines for maintenance treatment of juvenile bipolar disorder rely heavily on evidence from adult studies
and relatively brief trials in juveniles, leaving uncertainties about optimal long-term treatment. We aimed to systematically
review long-term treatment trials for juvenile bipolar disorder.
Methods: We analyzed data recovered by a systematic literature search using the PRISMA guidelines statement, through 2018,
for peer-reviewed reports on pharmacological treatments for juvenile bipolar disorder lasting ≥24 weeks.
Results: Of 13 reports with 16 trials of 9 treatments (18.8% were randomized and controlled), with 1773 subjects (94.4%
BD-I; ages 6.9–15.1 years), lasting 11.7 (6–22) months. Pooled clinical response rates were 66.8% (CI: 64.4–69.1) with drugs vs
60.6% (53.0–66.7) in 3 placebo-control arms. Random-effects meta-analysis of 4 controlled trials yielded pooled odds ratio
(OR) = 2.88 ([0.87–9.60], P = .08) for clinical response, and OR = 7.14 ([1.12–45.6], P = .04) for nonrecurrence. Apparent efficacy
ranked: combined agents >anticonvulsants ≥lithium ≥antipsychotics. Factors favoring response ranked: more attention
deficit/hyperactivity disorder, polytherapy, randomized controlled trial design, nonrecurrence vs response. Adverse events
(incidence, 5.50%–28.5%) notably included cognitive dulling, weight-gain, and gastrointestinal symptoms; early dropout rates
averaged 49.8%.
Conclusions: Pharmacological treatments, including anticonvulsants, lithium, and second-generation antipsychotics, may
reduce long-term morbidity in juvenile bipolar disorder. However, study number, quality, and effect magnitude were limited,
leaving the status of scientific support for maintenance treatment for juvenile bipolar disorder inconclusive.

Keywords: bipolar disorder, efficacy, juvenile, long-term, pharmacotherapy, treatment

Introduction

Juvenile bipolar disorder (jBD) is a life-long psychiatric illness associated with significant morbidity, disability, and increased mortality among those affected (Pfeifer et al., 2010; Goldstein et al., 2012; Kaplin et al., 2015). Once considered rare among juveniles, 50%–66% of adults diagnosed with BD report onset of illness in childhood or adolescence (Liu et al., 2011; Mohammad 2017). Epidemiological studies suggest a juvenile prevalence of BD of 1%–2% (Liu et al., 2011; Van Meter et al., 2011), or only moderately lower than in adults (Cox et al., 2014). BD ranks as the fourth leading cause of disability among adolescents worldwide,

and the associated suicide rate is 20–30 times higher than in the general population (Lee 2016; Kaplin et al., 2015).

A recent national survey of office-based American physicians revealed a 40-fold increase in prevalence of jBD diagnoses, from 0.0250% in 1994 to 1.003% in 2003 (40-fold increase) (Lee 2016; Mohammad 2017). Reported prevalence rates of jBD are higher in the United States than in most other countries. Factors contributing to variance in reported rates include sample ages, diagnostic criteria, ascertainment methods and information sources used, debated conceptualizations of the disorder in juveniles (especially in prepubertal children), and perhaps effects of medication exposure and environmental stressors (Soutullo et al., 2005; Goldstein et al., 2017). In European countries, diagnosis of jBD usually follows relatively narrow ICD-10 criteria compared with US preference for relatively broad DSM-IV or -5 criteria.

Compared with BD in adults, jBD patients reportedly spend more time symptomatically ill, especially in mixed states, or with rapid-cycling and subsyndromal symptoms as well as relatively severe behavioral disruption (Youngstrom et al., 2008; Birmaher et al., 2009; Goldstein et al., 2017; Mohammad 2017). The diagnosis, especially in prepubertal children, is challenging and made even more complicated by the common co-occurrence of other conditions, particularly attention deficit/hyperactivity disorder (ADHD), with overlapping symptoms (Youngstrom et al., 2008). Early onset of jBD is associated with relatively poor prognosis, underscoring the importance of early case identification and treatment (Ariza et al., 2009).

Since BD is a lifelong illness with high risk of relapse and sustained disability, effective prophylactic pharmacological treatment, specifically in the juvenile population, is an especially important component of treatment (Kowatch et al., 2003; Ariza et al., 2009; Kaplin et al., 2015). There are several published guidelines for long-term treatment of jBD. US Child and Adolescent Bipolar Foundation (2005) guidelines recommend mood-stabilizers (carbamazepine, lamotrigine, lithium, and valproate) and modern antipsychotics (olanzapine, quetiapine, and risperidone) as first-line treatments and their combinations as second-line regimens (Kowatch et al., 2005; Cox et al., 2014). UK National Institute for Health and Care Excellence (NICE 2006, 2018; Cox et al., 2014; Goodwin et al., 2016) guidelines recommend use of low doses of second-generation antipsychotics (SGAs) as a first choice for long-term jBD treatment, particularly agents with a low risk for weight-gain and hyperprolactinemia, and lithium alone or with valproate as secondary options. American Academy for Child and Adolescent Psychiatry (AACAP 2007) guidelines suggest SGAs be used as adjuncts or alternatives to lithium and valproate (McClellan et al., 2007; Cox et al., 2014). The American Academy for Child and Adolescent Psychiatry also expressed preference for agents with US-FDA regulatory approval specifically for treatment of jBD (Mohammad 2017; Bernstein 2018). The Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders proposed aripiprazole, lithium, and valproate as preferred options for long-term treatment of jBD (Yatham et al., 2018).

FDA-approved options for an acute manic episode in jBD include aripiprazole, asenapine, risperidone, or quetiapine for patients aged ≥10 years, and lithium or olanzapine for adolescents aged 12 or 13 to 18 years. No mood-altering anticonvulsant (carbamazepine, lamotrigine, or valproate) is currently FDA approved for any phase of jBD (Cox et al., 2014; Diaz-Caneja et al., 2014; French 2018). Lurasidone was approved in 2018 for treatment of major depressive episodes in BD-I disorder in juveniles aged 10–17 years (Bernstein 2018). In current clinical practice, maintenance or long-term treatment of jBD with prophylactic intent often involves the off-label use of antipsychotics and anticonvulsants.

The clinical importance of safe and effective long-term treatments for jBD motivated the present systematic review of specific pharmacological interventions for maintenance or prophylactic treatment of jBD. Given the paucity of relevant, blinded, and randomized controlled trials (RCTs), we also considered findings from "open-label," unblinded, or uncontrolled and nonrandomized but prospective trials with a minimum duration of 6 months.

Methods

Search Strategy

This systematic review followed Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (Liberati et al., 2009), carried out through February 2018, using PubMed, OVID MEDLINE, EMBASE, and PsycINFO databases, as well as clinicaltrials.gov and the WHO International Clinical Trials Registry, to identify peer-reviewed reports on maintenance pharmacological treatment of jBD with or without randomization and controls. We searched bibliographies of identified reports, including open-label studies and reviews, for references to additional studies. Authors and pharmaceutical companies involved in identified studies were contacted by telephone and email to seek clarifications and access to missing data.

The following search strategy was used across databases: search terms included "bipolar disorder, bipolar mania, bipolar depression, and child, pediatrics, adolescent, youth, and pharmacotherapy, antipsychotic, aripiprazole, asenapine, carbamazepine, divalproex, haloperidol, lamotrigine, lithium, lurasidone, olanzapine, oxcarbazepine, paliperidone, quetiapine, risperidone, topiramate, valproate, valproic, ziprasidone" and "long-term, maintenance, prophylaxis, and trial, double-blind, randomized controlled trial, RCT, open-label, naturalistic." PubMed searching was supplemented by using its "similar articles" function. The search strategy and retrieved reports were reviewed independently by 2 investigators (C.S.Y. and G.H.V.) to ensure comprehensive and accurate sampling; reports involving duplicate material were excluded in favor of first or most complete reports.

Retrieved titles and abstracts were screened independently by the same 2 investigators, followed by reviewing full texts of reports that seemed relevant. Inclusion criteria included peer-reviewed published reports of prospective studies (RCTs, uncontrolled trials, and naturalistic studies) evaluating lithium, anticonvulsants, SGAs, or their combinations for long-term (≥6 months) treatment of jBD with or without other co-occurring psychiatric diagnoses, based on Diagnostic and Statistical Manual of Mental Disorders criteria (III, IV, IV-TR, or 5; American Psychiatric Association, 1980, 2000, 2013). Accepted reports included at least a summary in English, ≥30 juvenile (youth) subjects aged ≤18 years and a minimum nominal trial duration of 6 months, with data on rates of response or treatment failures and on adverse events. Exclusion criteria included retrospective studies, chart reviews, case reports, studies lasting <6 months, and reports lacking data on rates of response, clinical change, or treatment failure.

Initially 111 publications were considered and reduced to 89 after excluding 22 documents with duplicate information; another 37 reports were excluded for lack of relevance based on screening their titles and abstracts, leaving 52 reports for full-text review. This process led to the exclusion of another 39
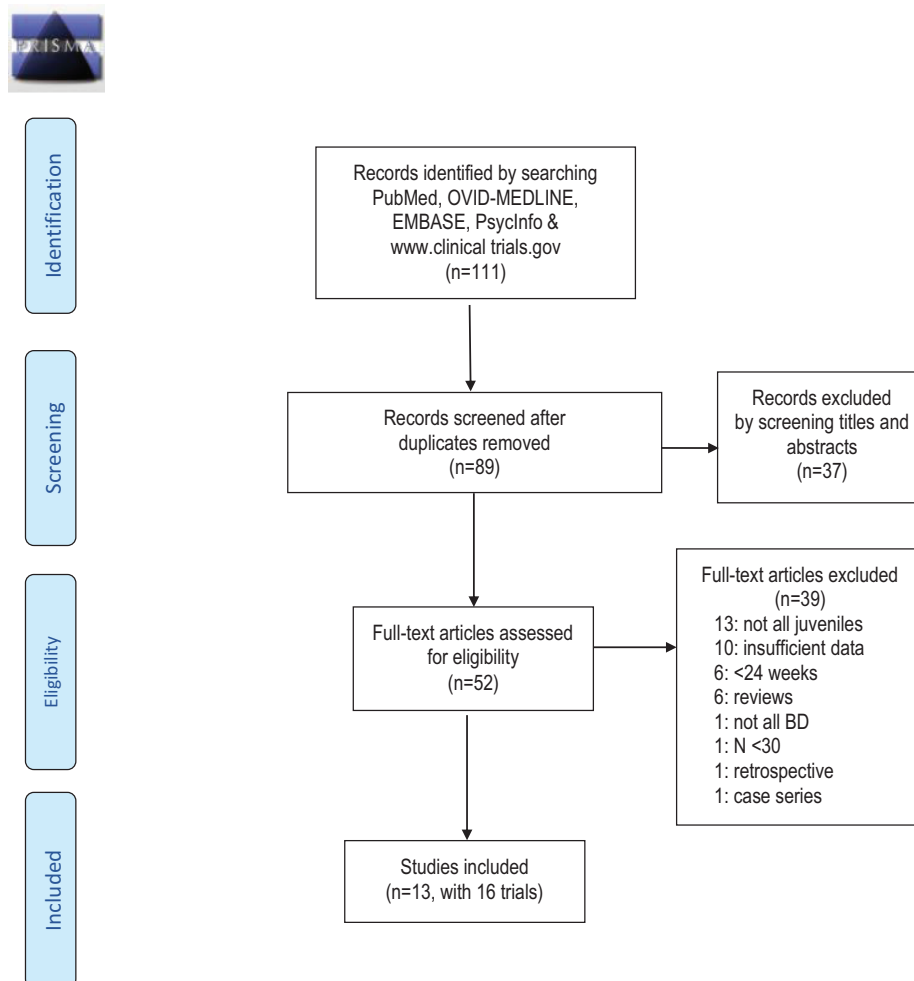
Figure 1. Summary of selection (flow diagram) for systematic searching of research literature databases, as recommended by the PRISMA program, for reports on long-term treatment of juvenile bipolar disorder subjects.

reports, leaving a final count of 13 (Figure 1). The 13 reports included 3 with 2 active-treatment arms, providing a total of 16 trials for systematic analysis, including 3 RCTs and 1 open trial with an untreated group, providing 4 trials for meta-analysis.

Data Recorded

The following information was extracted from each included report (by C.S.Y. and E.R.H.): author(s), publication year, drug(s) tested, number of study participants per trial arm, number or proportion responding to active treatments and controls, and corresponding counts of subjects experiencing at least 1 new illness episode. Efficacy as clinical treatment response was defined most often as achieving ≥50% reduction of intake Young Mania Rating Scale (Young, 1978) score plus a score <40 on the Children's Depression Rating Scale-Revised (Poznanski et al., 1985) and less often as achieving emotional stability based on clinical impression. Lack of a new episode of illness (nonrecurrence) was less often reported and was considered a secondary outcome measure for jBD subjects, who do not always follow an adult-like episodic course of illness (Geoffroy et al., 2014; Lee 2016).

Some reports provided data on the number or proportion of subjects who encountered a particular adverse event and those who discontinued treatment because of such events.

Adverse events were categorized as gastrointestinal, neurological, weight-gain, and others (including suicidal ideation or behavior). Events considered clinically severe included need for clinical intervention, medical hospitalization, or death.

Studies involving more than 1 independent, active-treatment arm were considered as separate trials (control arms could be compared with more than 1 active treatment). When the same drug was tested at more than 1 dose, we used mean outcome across doses (none of which differed significantly in outcomes) and report mean dose. For studies with an initial short-term, controlled phase followed by an open-label extension phase, we extracted data only for the longer phase.

Study quality was rated independently by 2 investigators (C.S.Y. and E.R.H.) and averaged using a US NIH scoring form (NHLBI 2017) based on 14 questions scored as yes (1) or no (0), with a maximum score of 14.0; studies scoring <5.0 were considered poor.

We also noted potential moderator factors that might influence treatment responses. These included: (a) mean age (<12 vs ≥12 years); (b) sex (<60% males vs ≥60% males); (c) presence of ADHD (≥70% vs <70% of subjects); (d) design (RCT vs uncontrolled); (e) nominal treatment duration (<12 vs ≥12 months); (f) drug type (anticonvulsant, lithium carbonate, antipsychotic, or their combinations); (g) drop-out rate for any reason (<50% vs ≥50%); (h) source of support (pharmaceutical manufacturers vs

research grants); (i) quality score (≥10 vs <10); and (j) reporting year (1990–2017).

Data were extracted independently by C.S.Y., E.R.H., and G.H.V.; any disagreements were resolved by consensus. We made efforts to obtain missing data by contacting authors of study reports and sponsoring pharmaceutical companies. Studies were excluded if sufficient information was not found.

Statistical Analysis

Rates of clinical response and nonrecurrence were pooled across all 16 trials to provide proportions of those with favorable outcomes among all subjects in each trial arm. Differences in these ratios were tested with contingency tables (χ^2). Data from the 3 RCTs (Findling et al., 2012, 2013a, 2015) and 1 other partially controlled trial (Strober et al., 1990) were tested conservatively with random-effects meta-analysis even if measures of inter-trial heterogeneity (Q or I^2 derived from Q-score) were nonsignificant, owing to the rarity of RCTs. Outcomes with active agents based on the 2 outcome measures (response and nonrecurrence) were compared by contingency table. Given so few RCTs, meta-regression was not employed, but candidate response-modifying factors were tested for their association with responders vs nonresponders by contingency tables. Effects of types of active treatments (anticonvulsants, antipsychotics, lithium, and their combinations; n = 3–5 trials each) were tested by ANOVA methods (t test), and combination treatments vs pooled responses to monotherapies were compared by contingency tables. Adverse events were ranked by mean reported incidence rates of individual events and by classes of effects (gastrointestinal, neurological, other) and tested for association by types of treatments by ANOVA for overall differences, with Fisher's post-hoc assessment of individual paired comparisons. Data are presented as means ± SD or with 95% confidence intervals (CI). Statistical analyses were based on commercial software (Statview.5 [SAS Institute, Cary, NC] for spreadsheets, and Stata-13 [StataCorp, College Station, TX] for computations).

Results

Studies Included

Of 111 reports originally considered, we included findings from 16 trials in 13 publications (Figure 1; 3 trials involved 2 active treatment arms) and summarized their salient characteristics (Table 1) (Strober et al., 1990; Pavuluri et al., 2004, 2005, 2006; Findling et al., 2005, 2012, 2013a, 2013b, 2015, 2016; Redden et al., 2009; Findling and Ginsberg 2014; Chang et al., 2017). Of a total of 1773 subjects, 94.4% were diagnosed as having BD-I; age averaged 12.4 (CI: 11.4–13.4) years, with an excess of boys (61.9% [57.3–66.6]). An average of 71.6% (62.2–81.1) of all subjects met diagnostic criteria for co-occurring ADHD. Only 3/16 trials (18.8%) were randomized, blinded, and placebo-controlled (RCTs) (Findling et al., 2012, 2013a, 2015); the other 13 were "open-label" (nonrandomized, uncontrolled, not blinded), though 1 included an untreated comparison group (Strober et al., 1990). Pharmaceutical sponsorship was identified in 9/13 (69.2%) trials. Dropout rates averaged 49.8% (32.6–67.0) and ranged from 0.00% (Pavuluri et al., 2004) or 2.94% (Pavuluri et al., 2005) to 90.0% (Findling et al., 2012) in trials lasting a nominal average of 11.7 (8.64–14.8) months (ranging from 6.0 (Pavuluri et al., 2004, 2005; Redden et al., 2009) to 22 months (Findling et al., 2012)). Overall study-quality scores averaged

7.92 (7.34–8.50) points, ranging from 5.50 (Chang et al., 2017) to 11.5 (Findling et al., 2013a) out of 14.

Treatment Outcomes

Treatment effects were measured as proportions (%) of subjects considered as showing clinical improvement ("response") or having no recurrences of new illness episodes (Table 2). For all 16 trials of active agents, the pooled clinical response rate (n/N) was 1040/1558 (66.8% [CI: 64.4–69.1]), and the pooled nonrecurrence rate was 114/201 (56.7% [49.6–63.7]). Response rates with drug treatments ranged from 26.7% (Findling et al., 2012) to 87.4% (Findling et al., 2015) of subjects in active treatment arms. Nonrecurrence rates with active agents ranged from 26.7% (Findling et al., 2012) to 79.1% (Findling et al., 2015). Nonrecurrence and clinical response rates were only moderately correlated (r = 0.490, P = .05; slope = +0.552 [CI: –0.01 to +1.12]).

The pooled response rate in placebo arms of the 3 RCTs was 109/180 (60.6% [53.0–66.7], and the corresponding nonrecurrence rate was 56/129 (43.4% [34.7–52.4]). The overall differences between active treatment and placebo-associated clinical response rates were greater for nonrecurrence (56.7%/43.4% = 1.31; χ^2 = 5.57, P = .02) than for clinical response (66.8%/60.6% = 1.10; χ^2 = 2.77, P = .10; Table 2).

In random-effects meta-analysis of data from 3 RCTs (2 with aripiprazole vs placebo, 1 adding lamotrigine or placebo to a mood-stabilizer or antipsychotic) and an open comparison of lithium vs nontreatment (Table 2), only nonrecurrence rates yielded a statistically significant difference between active drugs and controls (pooled OR = 7.14 [CI: 1.12–45.6], z = 2.08, P = .04) with substantial heterogeneity (I^2 = 66.3%). Instead, for 3 comparisons of responder rates in the 3 RCTs, the active treatment vs control contrast was not significant (pooled OR = 2.88 [0.87–9.60]; z = 1.73, P = .08), with high heterogeneity (I^2 = 74.5%).

Outcomes by Treatment Type

There were too few trials of each agent (n = 1–3/treatment) to support meaningful comparisons of individual treatments. However, types of treatments showed the following ranking by clinical response rate: combinations (3 trials), 82.7% [CI: 75.6–89.8]; anticonvulsants (5 trials), 53.2% [21.7–84.8]; lithium carbonate (3 trials), 51.1% [0–164]; SGAs (5 trials), 50.1% [21.7–78.6]; these differences were statistically weak (t = 1.93, P = .07; Figure 2). When combination treatments were compared with pooled data for all monotherapies, the combination treatments (anticonvulsant or lithium + an SGA) were highly significantly more effective than the pooled monotherapies (χ^2 = 25.4, P < .0001; Table 3). Moreover, comparison of the 4 types of treatment yielded significant superiority of combinations over other alternatives, ranking by rate of favorable response outcomes: combinations (82.9% [CI: 78.6–87.3]) > anticonvulsants (56.5% [38.2–74.9]) ≥ lithium (52.6% [33.5–71.7]) ≥ SGAs (56.2% [30.1–82.3]); these rates differed overall (t = 1.91, P = .045), and by Fisher post-hoc testing, all other monotherapies were inferior to combinations.

Factors Associated with Efficacy

As meta-regression was not feasible given the few RCTs available for meta-analysis, we considered several factors as potential effect-modifiers, as indicated by association with clinical

Table 1. Characteristics of Long-Term Treatment Trials for Juvenile Bipolar Disorder

Reports	Drugs	Mean Dose (mg/d)	Subjects (N)	BD-I (%)	Mean Age	Males (%)	Index Polarity	ADHD (%)	Design	Duration (mo)	Dropouts[a] (%)	Sponsor[b]	Study Quality
Strober et al., 1990[31]	Li	—	37+0	100	15.1	56.8	M	—	Open	19.5	—	—	6.50
Pavuluri et al., 2004a[32]	Li+RSP	750+0.75	17+0	100	12.1	64.7	M or Mx	82.4	Open	6.00	65.0	—	7.00
Pavuluri et al., 2004b[32]	VPA+RSP	925+0.70	20+0	100	12.1	65.0	M or Mx	75.0	Open	6.00	0.00	—	7.00
Findling et al., 2005a[33]	Li	—	30+0	93	10.3	70.0	M	66.7	Open	19.0	90.0	Grants	11.0
Findling et al., 2005b[33]	VPA	—	30+0	90	11.2	60.0	M	60.0	Open	19.0	90.0	Grants	11.0
Pavuluri et al., 2005[34]	VPA	950	34+0	100	12.3	61.8	M or Mx	76.5	Open	6.00	2.94	Grants	6.50
Pavuluri et al., 2006a[35]	Li+RSP	775+0.99	21+0	100	10.5	81.0	M or Mx	90.5	Open	13.0	18.4	Both	7.00
Pavuluri et al., 2006b[35]	Li	825	38+0	100	12.5	70.6	M or Mx	64.7	Open	13.0	18.4	Both	7.00
Redden et al., 2009[36]	VPA	1131	199+0	100	13.8	54.0	M	54.0	Open	6.00	51.8	Grants	6.00
Findling et al., 2012[37]	APZ	—	30+30	33	6.90	70.0	M	90.0	RCT	22.0	90.0	Pharma	10.0
Findling et al., 2013a[38]	APZ	18.4	146+64	100	13.3	—	M or Mx	—	RCT	7.50	67.6	Pharma	11.5
Findling et al., 2013b[39]	QTP	571	205+0	100	13.3	58.5	M	—	Open	7.25	45.0	Pharma	6.00
Findling & Ginsberg 2014[40]	CBZ	827	155+0	100	13.4	57.3	M or Mx	—	Open	6.50	58.0	Pharma	8.00
Findling et al., 2015[41]	LTG+AP/MS	—	87+86	100	13.5	58.0	Any	—	RCT	14.8	76.3	Pharma	10.5
Findling et al., 2016[42]	ASP	—	321+0	100	13.8	50.2	M or Mx	56.7	Open	13.2	51.1	Pharma	7.50
Chang et al., 2017[43]	LUR	53.8	223+0	100	14.3	51.1	D	—	Open	8.50	23.2	Pharma	5.50
16 Trials in 13 reports Totals or Means [CI]	9 Treatments—	—	1773	94.4 [85.9–100]	12.4 [11.4–13.4]	61.9 [57.3–66.6]	14/16 M or Mx	71.6 [62.2–81.1]	18.8% RCTs	11.7 [8.64–14.8]	49.8 [32.6–67.0]	9/13 Pharma	7.92 [7.34–8.50]

Treatments: AP antipsychotic, APZ aripiprazole, ASP asenapine, CBZ carbamazepine, Li lithium, LTG lamotrigine, LUR lurasidone, MS mood-stabilizer, QTP quetiapine, RSP risperidone, Rxs treatments, VPA valproate. Quality score: maximum = 14.0. ADHD = attention deficit/hyperactivity disorder; BD-I = type I bipolar disorder; D = depression; M = [hypo]mania; Mx = mania with mixed features. Reports labeled year-a and year-b are the same study with 2 active-treatment arms.

aReported dropout rates are highly variable, depending on definitions followed.

bCombination of grant and pharmaceutical support, so that 9/13 (69.2%) trials had some corporate support.

Table 2. Rates of Clinical Response and of Nonrecurrence During Long-Term Treatment of Juvenile Bipolar Disorder

| | | Clinical Response Rates | | | | Nonrecurrence Rates | | | |
| | | Drugs | | Control | | Drugs | | Control | |
Trials	Drugs	n/N	%	n/N	%	n/N	%	n/N	%
Strober et al., 1990[31]	Li	——	——	——	——	15/24	62.5	1/13	7.69[a]
Pavuluri et al., 2004a[32]	Li+RSP	14/17	82.4	——	——	——	——	——	——
Pavuluri et al., 2004b[32]	VPA+RSP	16/20	80.0	——	——	——	——	——	——
Findling et al., 2005a[33]	Li	19/30	63.3	——	——	12/30	40.0	——	——
Findling et al.,2005b[33]	VPA	19/30	63.3	——	——	10/30	33.3	——	——
Pavuluri et al., 2005[34]	VPA	25/34	73.5	——	——	——	——	——	——
Pavuluri et al., 2006a[35]	Li+RSP	18/21	85.7	——	——	——	——	——	——
Pavuluri et al., 2006b[35]	Li	17/38	44.7	——	——	——	——	——	——
Redden et al., 2009[36]	VPA	111/199	55.8	——	——	——	——	——	——
Findling et al., 2012[37]	APZ	8/30	26.7	1/30	3.33[b]	8/30	26.7	0/30	0.00[b]
Findling et al 2013a[38]	APZ	119/146	81.5	33/64	51.6[b]	——	——	——	——
Findling et al 2013b[39]	QTP	111/205	54.2	——	——	——	——	——	——
Findling & Ginsberg 2014[40]	CBZ	89/157	56.7	——	——	——	——	——	——
Findling et al., 2015[41]	LTG+AP/MS	76/87	87.4	75/86	87.2[b]	69/87	79.1	55/86	64.0[b]
Findling et al., 2016[42]	ASP	221/321	68.8	——	——	——	——	——	——
Chang et al., 2017[43]	LUR	177/223	79.4	——	——	——	——	——	——
16 trials in 13 reports Totals or Means [CI]	9 Treatments	1040/1558[c]	66.8 [64.4–69.1]	109/180[c]	60.6 [53.0–66.7]	114/201[d]	56.7 [49.6–63.7]	56/129[d]	43.4 [34.7–52.4]

Treatments: AP, antipsychotic; APZ, aripiprazole; ASP, asenapine; CBZ, carbamazepine; Li, lithium; LTG, lamotrigine; LUR, lurasidone; MS, mood-stabilizer; QTP, quetiapine; RSP, risperidone; VPA, valproate.
aNot treated but followed.
bPlacebo-controlled RCTs.
cFor response rates: $\chi^2 = 2.77$, $P = .10$.
dFor nonrecurrence rates: $\chi^2 = 5.57$, $P = .02$. By random-effects meta-analysis (as required by significant heterogeneity), for clinical response rates, OR = 2.88 (0.87–9.60), z = 1.73, P = .08; NNT = 5.8 (2.6 to >100); $I^2 = 74.5\%$; for nonrecurrence rates, OR = 7.14 (CI: 1.12–45.6); z = 2.08, P = .04; NNT = 3.3 (2.0–10.1); $I^2 = 66.3\%$.
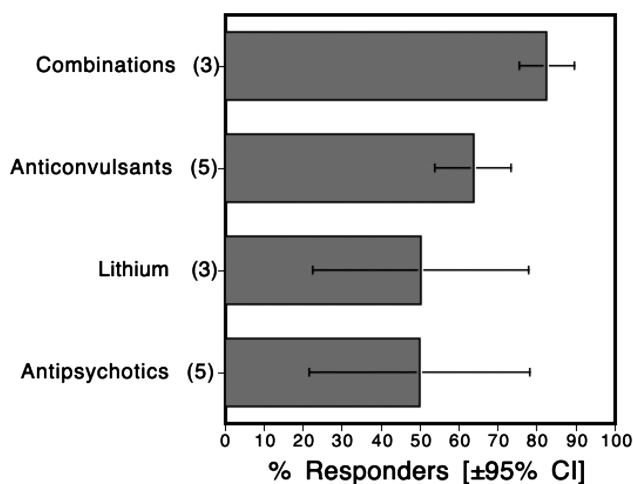
Figure 2. Mean rates of responding to types of experimental treatments for subjects diagnosed with juvenile bipolar disorder in 3–5 trials each (trial counts in parentheses) with 95% confidence intervals (CI). Outcomes rank: combinations of a mood-stabilizer (lithium or anticonvulsant with a second-generation antipsychotic [SGA]) >anticonvulsants (carbamazepine, lamotrigine, valproate) ≥lithium carbonate ≥short-acting SGAs (aripiprazole, asenapine, lurasidone, quetiapine, risperidone). The overall differences are significant (t = 1.91, P = .045), but by Fisher's post-hoc test only the combination treatments vs lithium or vs antipsychotics differed significantly (P = .02 and .01, respectively).

response rates across all 16 trials of active agents (Table 3). Associated with treatment response in rank-order of statistical significance were: more co-occurring ADHD (≥70% of subjects vs <70%); polytherapy vs monotherapy; RCTs vs nonrandomized, uncontrolled trials, and outcome as responder rates vs nonrecurrence rates. Additional factors not significantly associated with trial outcome included subject-age, nominal trial duration, proportion of boys vs girls, dropout rate, index episode polarity (most were initially manic), corporate vs grant support, and reporting year (Table 3).

Adverse Effects

We identified a total of 27 types of adverse effects across all 16 trials (Table 4). By mean incidence rates (% of subjects), the most commonly encountered were cognitive dulling (28.5% of treated subjects), weight-gain (28.0%), and nausea and vomiting (25.0%); least frequent were epistaxis, suicidal ideation, and diarrhea (5.50%–6.60%). By type of adverse effect, average incidence rates ranked: weight-gain (28.0% [CI: 16.4–39.7]), neurological symptoms (25.8% [15.5–36.1]), gastrointestinal symptoms (18.9% [14.9–23.0]), and miscellaneous symptoms (12.1% [9.95–14.2]); these differences are significant (t = 1.96, P = .01). By treatment type, mean adverse-effect risks ranked as follows: lithium (23.9% [18.1–29.7]), combinations (23.4% [19.0–27.7]), antipsychotics (20.0% [9.65–30.4]), and anticonvulsants (14.1% [10.6–17.7]); these differences are not statistically significant (t = 1.27, P = .19).

Discussion

This appears to be the first systematic review of peer-reviewed, research reports on the efficacy and tolerability of relatively long-term pharmacological treatments for jBD, including lithium, anticonvulsants considered to be mood-stabilizing, SGAs, and several of their combinations. Outcomes included

Table 3. Response Modifiers in Long-Term Treatment of Juvenile Bipolar Disorder

Factors	Trials (n)	Responders (n/N)	Responded (% [CI])	χ^2	P-value
ADHD				30.3	<.0001
≥70%	5	192/238	80.7 [75.1–85.5]		
<70%	6	395/648	61.0 [57.1–64.7]		
Treatment				25.4	<.0001
Polytherapy	4	124/145	85.5 [78.7–90.8]		
Monotherapy	12	916/1413	64.8 [62.3–67.3]		
Design				15.5	.0001
RCT	3	203/263	77.2 [71.6–82.1]		
Open	12	837/1295	64.6 [62.9–67.2]		
Outcome				7.95	.005
Response	15	1040/1558	66.8 [64.4–69.1]		
Nonrecurrence	5	114/201	56.7 [49.6–63.7]		

Abbreviations: ADHD, attention deficit/hyperactivity disorder; RCT, randomized controlled trial. Factors are in rank-order by statistical significance; other factors not significantly related to response rates included: subject age, nominal trial duration, proportion of boys vs girls, dropout rate, quality rating, pharmaceutical sponsorship vs grant-support, and reporting year. Greater response was associated with: more prevalent ADHD, combination treatments (lithium or mood-stabilizer+SGA) vs monotherapies, randomized placebo-controlled (RCT) vs uncontrolled design, outcome ratings of response vs nonrecurrence.

Table 4. Types and Rates of Adverse Events During Long-Term Treatment of Juvenile Bipolar Disorder

Symptoms	Rate (% of subjects)	95% CI
Cognitive dulling	28.5	14.2–42.8
Weight gain	28.0	16.4–39.7
Nausea and vomiting	25.0	18.3–31.7
Increased appetite	21.4	8.61–34.2
Headache	21.4	0.00–14.3
Tremor	21.3	11.3–31.3
Sedation/somnolence	20.7	13.6–27.8
Polyuria	20.7	0.00–60.1
Enuresis	20.2	0.00–50.2
Restlessness/akathisia	19.6	2.63–36.7
Abdominal pain	18.5	10.8–26.1
Fatigue	15.1	7.68–22.4
Flu-like symptoms	14.9	0.00–29.7
Extrapyramidal signs	14.1	0.99–27.2
Muscle/joint stiffness	13.1	0.00–28.9
Upper respiratory infection-like	10.4	4.63–16.2
Galactorrhea	10.0	—*
Decreased appetite	9.05	6.03–12.1
Insomnia	7.90	0.00–19.3
Dysgeusia	7.50	—*
Fever	7.33	0.00–20.4
Sore throat	7.10	0.00–15.6
Irritability	6.70	0.00–23.2
Dizziness	6.68	0.00–14.3
Diarrhea	6.60	1.53–11.7
Suicidal ideation	5.86	4.10–7.62
Epistaxis	5.50	—*

The overall risk of adverse events was 82.5% (CI: 77.5–87.5); 9.63% (5.50–13.8) were associated with treatment-discontinuation, and 3.55% (0.63–6.46) were considered clinically serious. *From single reports.

an average rate of clinical response of 66.8 [CI: 64.4–69.1] of subjects that was not significantly higher than the 60.6% [53.0–66.7] response in the only 3 placebo-control arms identified (χ^2=2.77, P=.10; Table 2). For nonrecurrence of new illness episodes, the pooled rate with drugs (56.7% [49.6–63.7]) was 13.3% superior to placebo (43.4% [34.7–52.4])—a moderately significant difference (χ^2=5.57, P=.02; Table 2).

Numbers of trials (1–3/treatment) were insufficient to support assessments of relative efficacy of particular treatments

(Table 1). However, pooled response rates for the 4 trials of combination treatments (lamotrigine, lithium, or valproate, usually with an SGA) yielded suggestively superior results to outcomes pooled across the monotherapy trials, despite the small number of trials (n=3) involving such combinations (Table 3). Nevertheless, the available data do not unequivocally support early use of combined treatments, and several international expert guidelines recommend starting treatment of jBD with single drugs and considering drug combinations only when more conservative options have failed (McClellan et al., 2007; Birmaher et al., 2013; Yatham et al., 2018).

It is unclear that recurrence rates are an appropriate outcome measure in trials for jBD, in that an adult-like episodic course of BD may not occur in prepubertal children though typically emerging more clearly in adolescence (Goldstein et al., 2012; Lee 2016). Alternative outcome measures include those considered as clinical responses addressed here, which do not require an episodic course with clear intervals of wellness or euthymia.

An important question is whether such trials are sufficiently long as to distinguish prophylactic benefits from early relapse prevention in jBD. Indeed, many of the studies involved short-term treatment (often controlled and randomized) of acute mania with open-label follow-up and so appear to be designed to test for short-term relapse prevention rather than prophylactic or maintenance treatment aimed at avoiding new illness recurrences. Recurrence intervals averaging 10.1–18.0 months have been found in adolescent BD patients who followed an episodic course (Geller et al., 2004; Jairam et al., 2004), and stable, inter-episode, intervals of a year or more have been reported in adults with BD, depending greatly on the status of treatment (Tondo et al., 2001; Snook et al., 2015). The British Association for Psychopharmacology recommended 12- to 24-month intervals of clinical stability as a criterion for considering reduction of ongoing maintenance treatment for BD (Goodwin et al., 2016). These observations suggest that in juveniles as in adults, prolonged observation for a year or longer is probably required to test adequately for ability of an experimental treatment to prevent recurrences. However, organizing and sustaining RCTs lasting a year or longer is logistically challenging, expensive, and risks high dropout rates. Notably, in the present data (Table 1), the longest trial (22 months) was associated with the highest dropout rate (90.0%; Findling et al., 2012). Nevertheless, long-term, controlled, maintenance trials for a year or longer have been feasible in adult BD (Keck et al.,

2007; Baldessarini et al., 2019) as well as in major depressive disorder (Sim et al., 2015) and can be carried out in jBD as well (Strober et al., 1990; Findling et al., 2005, 2016; Pavuluri et al., 2006; Chang et al., 2017).

An RCT design and use of a multi-psychotropic drug regime were associated with higher average response rates (Table 3). Another interesting but unexplained factor associated with higher rates of response was more co-occurring ADHD. This observation seems inconsistent with findings that jBD patients with co-occurring ADHD are less adherent as well as less responsive to treatment with lithium (Sim et al., 2015). We found no significant effect of sex, although boys diagnosed with jBD have been reported to be less adherent to prescribed treatment than girls (Drotar et al., 2007).

Adverse effects associated with pharmacological treatments for jBD varied markedly in prevalence. Although the overall risk for any adverse event was common at 82.5%, the risk of severe adverse effects was low (3.55%). The risk of early dropouts ascribed to adverse effects was moderate, at 9.63%, compared with an overall dropout rate of 49.8% (Tables 1 and 4). Rates for individual symptoms or syndromes ranged from 5.50% (epistaxis) to 28.5% (cognitive dulling), with relatively high rates of weight-gain (28.0%) and neurological symptoms (14.1%–21.4%) including akathisia (Table 4). Notably, clinically significant weight-gain (≥7%) was encountered in 18.9% (173/917) of the juveniles exposed to SGA monotherapy. Overall, combination treatments and lithium were associated with higher rates of adverse effects (23.4%–23.9%) than monotherapies with SGAs (20.0%) or mood-stabilizing anticonvulsants (14.1%).

Finally, the present findings do not provide strong support for the generalization that treatments effective for short-term treatment of acute jBD and adult BD may also be effective long-term with prophylactic or preventive intent in jBD, and indeed appear to represent mainly time-limited continuation trials likely to test for risk of relapse. More prolonged exposures would be expected to carry further risks, including effects encountered in maintenance treatment of adult BD, including metabolic syndrome with some SGAs, teratogenic effects of anticonvulsants with pregnancy, and valproate-associated polycystic ovarian syndrome. As well, the limited support of long-term effectiveness found in the present systematic review needs to be considered against the lack of regulatory approval of some of the proposed treatments for long-term or maintenance treatment of BD in adults or juveniles.

Limitations

This systematic review identified peer-reviewed research reports but not unpublished studies that might include additional negative findings. Diagnostic criteria for jBD, and the training and experience of screening evaluators varied among studies, adding to uncertainties. During maturation, clinical presentations of BD vary markedly, introducing complexity when data from subjects' different ages are pooled (Singh, 2008). Moreover, reported outcome measures may not be fairly comparable for all ages considered, particularly regarding prepubertal children and early and late adolescents, who often differ in the expression of an adult-like episodic course (Drotar et al., 2007; Freeman et al., 2015).

Having only 3 RCTs greatly limited the value of meta-analysis and precluded meaningful meta-regression. Only 3 trials (involving aripiprazole (Findling et al., 2012), lamotrigine (Findling et al., 2015), and lithium vs divalproex (Findling et al., 2005)) included data on the phase of illness at intake or with

new episodes arising during treatment. Most studies involved continuations of treatment trials for acute BD episodes, usually diagnosed as mania; only 1 (involving lurasidone [Chang et al., 2017]) evaluated treatment effectiveness solely in subjects presenting in bipolar depression. Therefore, adequate conclusions cannot be made regarding which treatments may have selective effects on preventing or reducing morbidity or risk of acute recurrences of depression or mania. Furthermore, for studies of maintenance treatment, the identified trials were of rather short duration; only one-half were designed to continue for 12 months or longer, and actual exposure times were not defined. That is, reported exposure times are estimates based on nominal targets rather than actual averaged individual times before early dropout from study protocols, which occurred in 49.8% and up to 90.0% of subjects (Table 1). Finally, of the 9/13 (69.2%) trials having pharmaceutical sponsorship, a majority (6/9 [55.6%]) involved positive responses, raising the possibility of reporting bias.

Conclusions

The present study found extraordinarily few well-designed, long-term trials of maintenance treatments for jBD of sufficient duration. It strongly encourages more well-designed, randomized, controlled trials of particular treatments and combinations, involving well-validated diagnostic criteria among juveniles of similar ages and without selection for initial responses in acute episodes and carried out over exposure times longer than 1 year.

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Statement of Interest

No author or immediate family member has a financial relationship with any commercial entity that might appear to present a potential conflict of interest in the material presented.

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