CHILDREN'S MENTAL HEALTH RESEARCH

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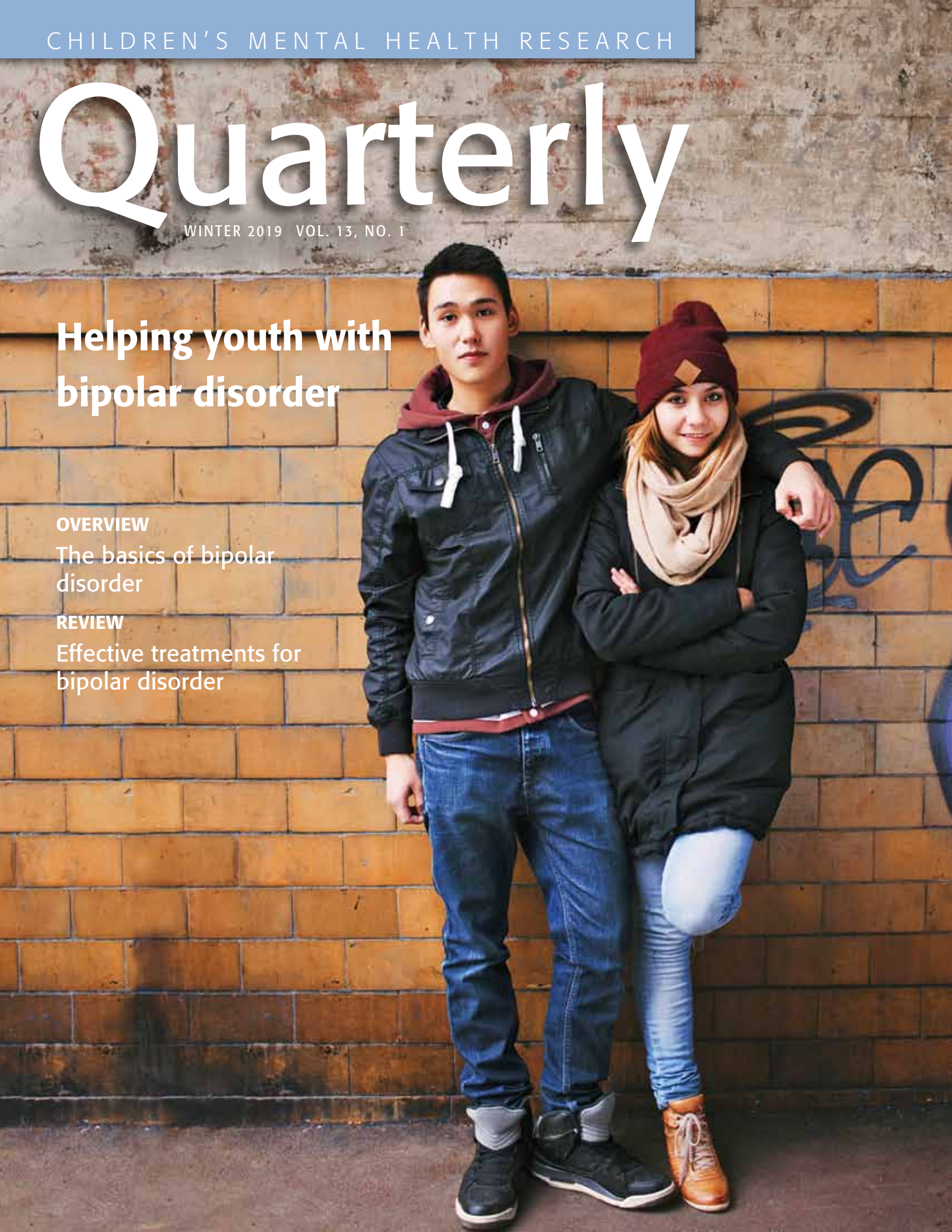

Helping youth with bipolar disorder

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Children's Health Policy Centre

About the Children's Health Policy Centre

We are an interdisciplinary research group in the Faculty of Health Sciences at Simon Fraser University. We focus on improving social and emotional well-being for all children, and on the public policies needed to reach these goals. To learn more about our work, please see childhealthpolicy.ca.

About the *Quarterly*

We summarize the best available research evidence on a variety of children's mental health topics, using systematic review and synthesis methods adapted from the *Cochrane Collaboration* and *Evidence-Based Mental Health*. We aim to connect research and policy to improve children's mental health. The BC Ministry of Children and Family Development funds the *Quarterly.*

Quarterly Team

Scientific Writer
Christine Schwartz, PhD, RPsych

Scientific Editor
Charlotte Waddell, MSc, MD, CCFP, FRCPC

Research Manager
Jen Barican, BA, MPH

Senior Research Assistant
Donna Yung, BSc, MPH

Production Editor
Daphne Gray-Grant, BA (Hon)

Copy Editor
Naomi Pauls, MPub

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This Issue

NEXT ISSUE

Celebrating 50 issues of the *Quarterly*

Anniversaries offer a time for celebration and reflection. To mark the 50th issue of the *Quarterly*, we highlight the value of 50 important lessons.

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How to Cite the *Quarterly*

We encourage you to share the *Quarterly* with others and we welcome its use as a reference (for example, in preparing educational materials for parents or community groups). Please cite this issue as follows:

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OVERVIEW

The basics of bipolar disorder

Bipolar disorder is very rare in young people – below 1%.

When diagnosing a young person with bipolar disorder, practitioners need to use standardized criteria such as those outlined in the *Diagnostic and Statistical Manual of Mental Disorders-5* or the *International Classification of Diseases-11*.[1–2] Two types of disorder are recognized: bipolar I, which is more serious, and bipolar II.

To be diagnosed with bipolar I, a young person must have experienced a distinct manic episode involving both the following symptoms most of the day and nearly every day for seven days or more:

- Persistently and abnormally elevated, expansive or irritable mood; *and*
- Persistently and abnormally increased energy and activity.[1]

As well, at least three of the following symptoms must be present to a significant degree and must represent a marked change from the young person's usual presentation:

- Inflated self-esteem
- Decreased need for sleep
- Increased talking or pressured speech
- Racing thoughts
- Distractibility
- Increased goal-directed activities or psychomotor agitation
- Excessive involvement in activities with high potential for negative outcomes (e.g., taking risks)[1]

Significant controversies about bipolar disorder in children began in the 1990s.

The mood disturbance must be severe enough to markedly affect the young person's functioning. Psychosis may also develop. Further, the influence of substances or a medical condition must also be ruled out. Note that while some young people with bipolar disorder experience major depressive episodes, they are not required for a diagnosis of bipolar I.

To be diagnosed with bipolar II, in comparison, a young person must meet criteria for a "hypomanic" episode and for a major depressive episode.[1] A hypomanic episode is identical to a manic episode except that it lasts only four days rather than seven.[1] (Please see the Fall 2017 *Quarterly* for more information on diagnosing major depressive disorder.)

Resolving controversies

Significant controversies about bipolar disorder in children began in the 1990s, when dramatic increases in diagnoses fuelled questions and debates.[3–4] Since then, however, the controversy has waned. This waning has been due, in part, to research illuminating the likely cause for the diagnostic increases. Specifically, a review of diagnostic rates between 1985 and 2007 found that presumed prevalence increases did not indicate a

real increase in prevalence. Rather, they mainly reflected the fact that previously, young people were rarely diagnosed with bipolar disorder.[4] More recent data from nearly 200 countries continue to show that bipolar disorder is very rare in young people — below 1%.[5]

Why comprehensive assessment remains critical

Still, bipolar disorder continues to be a condition that is susceptible to both overdiagnosis and underdiagnosis.[4] Both situations can cause harm. Overdiagnosis can lead to the prescription of unnecessary medications as well as negative labelling and stigma. Conversely, underdiagnosis can result in children not getting help when they need it. Practitioners therefore need to be particularly careful when assessing children for bipolar disorder.

Practitioners need to be particularly careful when assessing children for bipolar disorder.

Practitioners also need to be prepared if young people or parents/caregivers raise the issue of bipolar disorder. For example, they may express concern about mood swings. Yet careful questioning could lead to other explanations — such as "mood swings" reflecting typical mood variations for adolescents, or reflecting reactions to stressors or adverse experiences.

The typical age of onset for bipolar disorder provides another reason for being particularly cautious before making a diagnosis. For bipolar I, the average age of onset for a manic, hypomanic or major depressive episode is about 18 years.[1] This suggests that younger children are far less likely to meet diagnostic criteria for bipolar disorder.

Following careful and comprehensive assessment, when young people do have bipolar disorder, effective treatments are critical. In the Review article that follows, we identify effective interventions for these young people, including new psychosocial interventions..

Effective treatments are critical when a young person has bipolar disorder.

REVIEW

Effective treatments for bipolar disorder

Parents play an essential role in supporting young people with bipolar disorder.

Young people who have bipolar disorder need effective treatment options. To identify the best options, we reviewed high-quality intervention studies published over the past two decades — including evidence on new psychosocial treatments.

To identify interventions, we conducted a systematic review. We built quality assessment into our inclusion criteria to ensure that we reported on the best research available. In particular, we required all studies to measure core bipolar symptoms, namely mania or hypomania, and to use randomized controlled trial (RCT) evaluation methods. We then searched for RCTs evaluating interventions for childhood bipolar disorder published in the past 10 years. We also reviewed previous *Quarterly* issues to identify older studies that met our current inclusion criteria. This process enabled us to address the best RCT evidence from the past 20 years. (Please see the Methods section for more details on our search strategy and inclusion criteria.)

We retrieved and evaluated 50 studies. Twelve RCTs met our inclusion criteria; of these, six assessed medications, five assessed psychosocial interventions, and one assessed a dietary supplement. Five medications were evaluated in six trials: aripiprazole,[6] asenapine,[7] lithium (two RCTs),[8–9] quetiapine (adjunctive to divalproex, an extended-release form of valproic acid)[10] and risperidone.[11] Three psychosocial interventions were evaluated (typically adjunctive to medication) in five trials: Multifamily Psychoeducational Psychotherapy (MF-PEP),[12] Child- and Family-Focused Cognitive-Behavioural Therapy (CFF-CBT),[13] and Family-Focused Therapy (three RCTs).[14–16] Flax oil, a dietary supplement, was evaluated in one trial.[17] Given the focus of our review, we limited our reporting to outcomes associated with bipolar disorder symptoms and related overall functioning, including quality of life.

Medication studies

In five of the six medication RCTs, all children were diagnosed with bipolar disorder. In the other RCT, 68% were diagnosed with bipolar disorder; the rest were diagnosed with major depressive disorder *and* deemed at risk for bipolar disorder, because, for example, they had exhibited bipolar symptoms after using an antidepressant.[8] All youth in this other study also had a secondary substance use disorder.

The RCTs varied in their dosing approaches. For aripriprazole and asenapine, dosing was fixed.[6–7] For lithium, quetiapine and risperidone, dosing was flexible, varying with therapeutic response.[8–11] As well, aripiprazole and risperidone were tested at two

Translating drug names

Most medications are available in both generic and proprietary versions. Here we list the names that the drugs are sold under in Canada, if available.

Bipolar Medications[18]

Medication class	Generic name	Brand name
Atypical antipsychotic	Aripiprazole*	Abilify
Atypical antipsychotic	Asenapine**	Saphris
Mood stabilizer	Lithium*	Not applicable
Atypical antipsychotic	Lurasidone	Latuda
Atypical antipsychotic	Risperidone	Risperdal
Atypical antipsychotic	Quetiapine	Seroquel

* Approved by Health Canada for the treatment of bipolar disorder in youth.
** Not available for sale in Canada.

Why did researchers study quetiapine adjunctively?

Researchers assessed the effectiveness of quetiapine as an adjunctive treatment to divalproex after reviewing data from some less rigorous studies which found that while divalproex helped some young people, many still failed to respond to it.[10] These researchers wanted to determine whether adding an atypical antipsychotic (quetiapine) to a mood stabilizer (divalproex) decreased manic symptoms and improved response rates.[10] Notably, we could not find any high-quality evidence supporting the use of divalproex for treating bipolar disorder in young people. Although we did assess six randomized controlled trials evaluating valproic acid and its derivatives, including divalproex, none met our inclusion criteria.

different doses and asenapine was tested at three different doses.[6–7, 11] For the quetiapine RCT, meanwhile, both intervention and control groups received divalproex, because researchers were evaluating quetiapine adjunctively to this medication.[10] (For why they did so, see the sidebar at left) All medications were compared to placebo.

Notably, pharmaceutical companies were involved in all the medication RCTs, including companies providing medications for the study, or study authors working for or holding stocks in the companies. Pharmaceutical companies had even greater involvement in two RCTs. This involvement included providing writing and editorial support for the risperidone trial, and providing direct oversight and participating throughout the asenapine trial.[7, 11] The second lithium trial stood out as being the only one not funded by a drug company; however, some authors on this trial still had pharmaceutical company affiliations.[9] Table 1 summarizes the medication RCTs.

Table 1: Medication Studies

Medication	Dose* and duration**	Sample size	Ages (Years)	Country
Aripiprazole [6]	10 or 30 mg for 4 weeks	296	10 – 17	United States
Asenapine [7]	5, 10 or 20 mg for 3 weeks	404	10 – 17	United States + Russia
Lithium I [8]	600 – 2,400 mg for 6 weeks	25	12 – 18	United States
Lithium II [9]	600 – 3,600 mg for 8 weeks	81	7 – 17	United States
Quetiapine† [10]	50 – 450 mg for 6 weeks	30	12 – 18	United States
Risperidone [11]	0.5 – 2.5 mg or 3 – 6 mg for 3 weeks	169	10 – 17	United States

* Doses reflect daily total, with some being given in single and others in multiple doses. As well, doses are not comparable among medications.
** Duration includes total time on medication regardless of dose. In many studies, dose was titrated over time.
† Young people in both quetiapine and placebo groups received divalproex as the primary medication.

Psychosocial studies

We identified five new studies assessing psychosocial interventions, typically adjunctive to medications, for bipolar disorder in young people. In three of the five RCTs — assessing Child- and Family-Focused CBT (CFF-CBT) and Family-Focused Therapy I and III — all participants were diagnosed with bipolar disorder.[13–14, 16] In the RCT assessing Multifamily Psychoeducational Psychotherapy (MF-PEP), 70% had bipolar disorder while the others had depression or dysthymia.[12] In the RCT assessing Family Focused Therapy II, 73% had bipolar disorder while the others had depression or cyclothymia (which involves multiple periods of hypomanic symptoms and depressive symptoms that do not meet criteria for either hypomanic or depressive episodes).[15]

The psychosocial interventions all contained similar content. In particular, they provided education about bipolar disorder and taught skills to young people and their parents, including managing mood symptoms, problem-solving and communicating strategies.[12–16, 18] Examples of specific interventions included teaching about the connection between thoughts, feelings and actions; practising active listening; and generating solutions to problems and evaluating the pros and cons of each.[12, 15]

However, intensity of the interventions varied considerably, as they ranged from 12 to 21 sessions. The comparison groups also varied, ranging from a waitlist control group for MF-PEP, treatment as usual (18 unstructured sessions) for CFF-CBT, and family education sessions for Family-Focused Therapy (three for versions I and III, and one or two for version II). Most young people in the psychosocial RCTs were also taking medications for their bipolar disorder — in both the intervention and comparison groups. Table 2 summarizes the psychosocial RCTs.

Table 2: Psychosocial Intervention Studies

Program	**Delivery**	**Sample size**	**Ages** (Years) **Country**
Multifamily Psychoeducational Psychotherapy (MF-PEP)[12]	8 parent + 8 youth sessions* over 8 weeks	166	8 –11 United States
Child- and Family-Focused Cognitive-Behavioural Therapy (CFF-CBT)[13]	6 family sessions, 3 parent sessions + 3 youth sessions + 6 booster sessions** over 9 months	69	7 –13 United States
Family-Focused Therapy I[14]	21 family sessions over 9 months†	58	12 –17 United States
Family-Focused Therapy II[15]	12 family sessions over 4 months†	40	9 –17 United States
Family-Focused Therapy III[16]	21 family sessions over 9 months†	145	12 –18 United States

* Both parent and youth sessions used a group format. Each session began and ended with parent and youth together.
** Format of booster sessions varied according to families' individual goals.
† Families could request additional sessions as needed.

Dietary supplement study

We also accepted one study on a dietary supplement. In this flax oil RCT, all participants were diagnosed with bipolar disorder.[17] (The authors chose to evaluate flax oil because it contains alpha linolenic acid, which, they hypothesized, might stabilize mood.) Dosing was titrated so young people could receive up to 12 grams (or 12.9 mL) of flax oil per day during the 16-week trial.[17] The control was olive oil. Approximately two-thirds of participants were also being prescribed medications for their bipolar disorder. Table 3 summarizes this RCT.

Table 3: Dietary Supplement Study

Supplement	**Dose and duration**	**Sample size**	**Ages** (Years)	**Country**
Flax oil[17]	Up to 12 grams (12.9 mL) for 16 weeks	51	6 –17	United States

Medication outcomes

Aripiprazole was tested at doses of 10 mg and 30 mg daily. Both doses significantly reduced bipolar severity.[6] Both doses also reduced manic symptoms, according to child, parent and clinician-observer reports. In fact, 45% of those taking 10 mg of aripiprazole and 64% taking 30 mg experienced reductions of 50% or more in manic symptoms by observer report, compared with 26% for controls. But the medication had no impact on depression — with one exception. Parent-reported depression symptoms were significantly reduced for those taking 10 mg daily (but not for those taking 30 mg). Finally, young people's overall functioning significantly improved on both aripiprazole doses, yet no differences were found for measures of quality of life compared to controls.

Asenapine was tested at three different daily doses (i.e., 2.5 mg, 5 mg and 10 mg). All three doses significantly reduced bipolar severity and reduced manic symptoms by observer reports.[7] Specifically, 42% of

What medications has the Canadian government approved?

Health Canada is the federal government agency that approves all drugs for use in Canada and indicates the approved terms of their use. Among the five medications we evaluated, only two are approved for treating bipolar disorder in young people. Aripiprazole is approved for treating manic or mixed episodes for 13- to 17-year-olds.[18] And lithium is approved for treating manic episodes for those aged 12 years and older.[18] In contrast, Health Canada specifically states that asenapine, risperidone and quetiapine are not indicated for use in people younger than 18. (Divalproex, another medication used in the trials we assessed, is also not approved for use in people younger than 18.)

youth on the 2.5 mg dose, 54% on 5 mg and 52% on 10 mg experienced reductions of 50% or more in manic symptoms, compared to only 28% of controls.

Both lithium RCTs produced mixed results. In the lithium I trial, there was no difference on a combined measure of manic and depressive symptoms for young people taking lithium or placebo.[8] However, participants taking lithium had better overall functioning than controls.

In comparison, in the lithium II trial, this medication resulted in fewer manic symptoms compared with placebo.[9] These findings included reduced overall manic symptoms (with moderate effect size; Cohen's $d = 0.53$) as well as manic symptom improvement (with 47% of those on lithium being rated as very much or much improved, compared with only 21% of controls). However, lithium did not significantly outperform placebo regarding manic severity, depressive symptoms or overall functioning.

Researchers have made progress in identifying interventions to help young people with bipolar disorder.

Quetiapine used adjunctively with divalproex showed one relevant benefit. The two medications together significantly reduced manic symptoms when compared with placebo plus divalproex.[10] In fact, 87% of those taking both medications experienced reductions of 50% or more in manic symptoms, compared with only 53% of those on placebo plus divalproex. However, there was no difference between the groups regarding depressive symptoms or overall functioning.

Finally, risperidone showed benefits at both lower and higher dose ranges (i.e., 0.5 to 2.5 mg and 3 to 6 mg total daily dose). Both ranges significantly reduced bipolar severity and manic symptoms.[11] Specifically, 59% of those on lower doses and 63% on higher doses experienced reductions of 50% or more in manic symptoms, compared with only 26% for controls. There was, however, no difference between the groups for depressive symptoms.[11]

There are now promising new psychosocial treatments for bipolar disorder.

Table 4 summarizes the outcomes for all six medication RCTs. Importantly, however, as also detailed in Table 4, all medications were associated with significant side effects.

Table 4: Medication Outcomes at Post-test

Medication	Outcomes	Side effects* and discontinuation rates
Aripiprazole[6]	↓ Bipolar disorder severity ↓ Manic symptoms (3 of 3) ↓ Manic severity ↓ Depressive symptoms (1 of 3)** NS Depressive severity ↓ Problems with overall functioning NS Quality of life	32% Any extrapyramidal symptom (movement problems including muscle spasms, rigidity + tremors) 29% Decreased prolactin (hormonal change) 23% Drowsiness 20% Extrapyramidal disorder (characterized by changes in muscle tone + movement) 6% Discontinued due to adverse events
Asenapine[7]	↓ Bipolar disorder severity ↓ Manic symptoms	49% Drowsiness, sedation + excessive sleep 22% Oral numbness + taste distortions 6% Discontinued due to adverse events
Lithium I[8]	NS Manic + depressive symptoms ↓ Problems with overall functioning	Thirst Excessive urination Nausea/vomiting Dizziness All four side effects were experienced by significantly more youth on lithium than placebo. Authors did not report the percentage of young people experiencing them nor the discontinuation rate.
Lithium II[9]	↓ Manic symptoms (2 of 2) NS Manic severity NS Depressive symptoms NS Problems with overall functioning	45% Nausea 43% Vomiting 32% Tremor 28% Diarrhea 28% Excessive thirst 26% Frequent urination 23% Dizziness 17% Elevated thyroid-stimulating hormone (hormonal change) 0% Discontinued due to adverse events‡
Quetiapine†[10]	↓ Manic symptoms NS Depressive symptoms NS Problems with overall functioning	80% Sedation 47% Gastrointestinal irritation 47% Headache 47% Increased prolactin (hormonal change) 33% Dizziness 33% Dry mouth 27% Nausea/vomiting 0% Discontinued due to adverse events
Risperidone[11]	↓ Bipolar disorder severity ↓ Manic symptoms NS Depressive symptoms	50% Drowsiness 39% Headache 24% Fatigue 12% Discontinued due to adverse events

* Experienced by ≥20% of those on medication, or by significantly more in the intervention group for studies that appropriately tested for statistical significance.
↓ Statistically significant improvements for medication over placebo.
** Statistically significant for 10 mg dose but not 30 mg.
NS No statistically significant difference between medication and placebo.
† Those in both quetiapine and placebo groups were given divalproex as the primary medication.
‡ Although 11.3% of participants stopped taking lithium, study authors did not deem discontinuation as being due to adverse events.

Psychosocial intervention outcomes

Each of the new psychosocial interventions showed benefits, albeit mixed or modest in some cases. For Multifamily Psychoeducational Psychotherapy, at 10-month follow-up, mania and depressive symptoms (assessed in a single measure) were significantly less severe for intervention participants compared with controls.[12]

Child- and Family-Focused CBT, at post-test, showed mixed outcomes, with no differences regarding bipolar severity or manic symptoms for intervention participants compared with controls.[13] However, depressive symptoms decreased according to parent ratings (although not practitioner ratings). As well, intervention participants had significantly higher overall functioning than controls. (Control youth, notably, received 18 unstructured therapy sessions for bipolar symptoms, a relatively intensive level of control intervention that may have affected the findings.)[13]

Family-Focused Therapy I also showed mixed outcomes. For time spent free of significant *manic/hypomanic* symptoms, no significant differences were reported between intervention and control groups over the two-year study period. However, for time spent free of prominent *depressive* symptoms, the intervention group did better than controls (52.6 vs. 48.3 weeks).[14]

The only dietary supplement trial that met our inclusion criteria failed to show benefits.

For Family-Focused Therapy II, intervention youth experienced significantly fewer weeks of prominent manic, hypomanic and depressive symptoms compared with controls. Specifically, over the one-year study period, intervention youth were free of mood symptoms for 26.8 weeks, versus 19.5 for controls.[15]

In contrast, Family-Focused Therapy III produced no beneficial outcomes related to bipolar disorder.[16] Specifically, intervention and control participants did not differ in the number of weeks it took them to recover from manic or depressive symptoms over the two-year study period. (Recovery was defined as experiencing at least eight consecutive weeks with no more than minor mood symptoms.) Table 5 summarizes the outcomes for all five psychosocial RCTs.

Table 5: Psychosocial Intervention Outcomes*

Program	Follow-up	Outcomes
Multifamily Psychoeducational Psychotherapy (MF-PEP)[12]	10 months	↓ Manic + depressive symptom severity
Child- and Family-Focused Cognitive-Behavioural Therapy (CFF-CBT)[13]	Post-test	NS Bipolar disorder severity NS Manic symptoms ↓ Depressive symptoms (1 of 2) ↓ Problems with overall functioning
Family-Focused Therapy I[14]	15 months**	NS # of weeks with prominent manic/hypomanic symptoms ↓ # of weeks with prominent depressive symptoms
Family-Focused Therapy II[15]	8 months**	↓ # of weeks with prominent manic, hypomanic or depressive symptoms NS # of weeks until recovery from manic/hypomanic symptoms
Family-Focused Therapy III[16]	15 months**	NS # of weeks until recovery from depressive symptoms

* Majority of participating youth were also taking medications to treat their bipolar disorder.
↓ Statistically significant improvements for intervention over comparison.
NS No statistically significant difference between intervention and comparison.
** Rather than being assessed solely at follow-up, outcomes were evaluated over the entire study duration.

Dietary supplement outcomes

The only dietary supplement trial that met our inclusion criteria failed to show benefits. As shown in Table 6, flax oil did not significantly differ from olive oil (the placebo) for any bipolar-related outcome at post-test.[17]

Table 6: Dietary Supplement Outcomes at Post-test

Supplement	Outcomes
Flax oil[17]	NS Bipolar disorder severity NS Manic symptoms NS Depressive symptoms NS Problems with overall functioning

NS No statistically significant difference for flax oil over placebo.

There are effective treatments

Our review affirms that there are effective treatments for bipolar disorder. Among the medications, aripiprazole and lithium stood out. Aripiprazole significantly reduced the severity of bipolar disorder in general and reduced manic symptoms in particular. It also improved overall functioning.[6] And lithium reduced manic symptoms while improving overall functioning.[8–9] Health Canada has also approved both these medications for treating bipolar disorder in youth.[18] Still, both medications have significant side effects, outlined in Table 4, and therefore require close monitoring when prescribed.[6, 8–9, 14–15] Although the other three medications — asenapine, quetiapine (adjunctive to divalproex) and risperidone — showed some benefits, they are not approved by Health Canada for treating bipolar disorder in young people. They also led to significant side effects.

Medications can dramatically reduce symptoms and improve young people's functioning.

Our review also found research evidence on new psychosocial treatments with considerable promise for young people with bipolar disorder. These interventions were delivered in the community and were relatively brief, ranging from 12 to 21 sessions over two to nine months — qualities likely making them appealing to youth and families. As well, each program had multiple benefits. MF-PEP reduced both manic and depressive symptom severity.[12] CFF-CBT reduced depressive symptoms and improved overall functioning.[13] And Family-Focused Therapy decreased the duration of depression in one study and decreased the duration of manic, hypomanic and depressive symptoms in another.[14–15] While psychosocial interventions were used alongside medications in these trials, our findings suggest important added benefits for young people over medications alone — particularly in addressing depressive symptoms.

The one RCT on a dietary supplement showed that flax oil was not helpful in treating bipolar disorder in young people.[17] This supplement is therefore not recommended.

Implications for practice and policy

Researchers have made progress over the past 20 years in identifying interventions to help young people with bipolar disorder. While more RCTs are needed, particularly on medications and their side effects, new psychosocial interventions show considerable promise alongside medications. Our findings suggest five implications for practitioners and policy-makers.

- *Provide long-term supports.* Bipolar disorder is a long-term condition. While it may wax and wane, young people with this disorder still need intensive and comprehensive ongoing health, social and other supports.
- *Use medications wisely.* Most young people with bipolar disorder will need medication to manage this disorder. Practitioners, in collaboration with young people and their families, need to carefully choose which medication to use. Aripiprazole and lithium should be considered first, given their evidence of effectiveness and their approval by Health Canada. (While asenapine, risperidone and quetiapine, adjunctive to divalproex, also reduced manic symptoms, Health Canada has not approved these medications for treating bipolar disorder in people younger than 18.) Practitioners who prescribe any medications must carefully monitor the responses and also the emergence of side effects, so these, too, can be managed. As well, using lowest possible doses to achieve good clinical effects can help to minimize side effects. Minimizing side effects can also help to reduce the high rates of young people with bipolar disorder who stop their medications because of side effects. Beyond this, new research is needed that does not have pharmaceutical company funding and involvement.
- *Offer psychosocial treatment as well as medication.* The three effective psychosocial treatments provided education about bipolar disorder and taught youth and their parents skills for managing mood symptoms, solving problems and communicating better. While more research is needed, these

interventions still show much promise and could be implemented now. Once a young person's symptoms are stable enough for them to participate in a psychosocial intervention, practitioners can be guided by the presenting concerns in deciding which one to suggest. CFF-CBT is most likely to help with managing depression, while MF-PEP and Family-Focused Therapy are most likely to help with managing both mania and depression.

- *Support practitioners to offer effective psychosocial treatments.* Because the effective psychosocial treatments have only recently been evaluated for treatment of bipolar disorder, their availability is likely limited. For this reason, policy-makers may need to provide supports for practitioners to learn these interventions. To facilitate this process, the developers of the psychosocial treatments have published books describing the interventions.
- *Discourage ineffective interventions.* Some young people and their families prefer not to use medications to treat bipolar disorder and seek other options. This reaction is understandable, particularly given the negative side effects and the fact that medications need to be used long term. Yet the only dietary supplement studied that met our criteria — flax oil — was not effective. Anyone expressing an interest in dietary supplements should be given this information. As well, Health Canada needs to ensure that companies marketing and selling these products do not make misleading or unproven claims about their effectiveness — and that potential harms are also carefully assessed, as with any drug.

Receiving a bipolar diagnosis can cause much stress and apprehension for young people and for their families — understandably, given the potential severity of the symptoms as well as the long-term nature of the condition. As well, all of the medications recommended to treat bipolar disorder have side effects. Still, medications can dramatically reduce symptoms and improve young people's functioning. Also, positive results from trials of new psychosocial treatments give reason for hope. Young people and their families should be given the message that bipolar disorder can be managed — and that many people with this disorder have gone on to thrive and to make important contributions, according to their abilities and gifts.

What are the medication options for depressive episodes?

Depression is often part of bipolar disorder in young people — and it can be particularly severe. While psychosocial treatments such as cognitive-behavioural therapy (CBT) are effective, engaging in CBT can be difficult when bipolar symptoms (including depression) are particularly acute or intense. At the same time, typical antidepressant medications can make bipolar disorder worse.[20] Therefore, medications options are needed for young people with bipolar disorder who have depression.

Researchers recently evaluated the medication lurasidone as a treatment for depression among youth with bipolar disorder.[21] Researchers conducted a six-week randomized controlled trial (RCT) including 350 young people from 11 countries. (This RCT did not meet criteria for our review because it did not assess manic or hypomanic outcomes. Like many studies in our review, the drug company provided funding and some research staff for the study.) This RCT found that for young people with bipolar disorder, lurasidone led to significantly fewer depressive symptoms than controls, with a moderate clinical impact (Cohen's $d = 0.45$). Side effects were common, with 64% of participants reporting at least one. Health Canada has approved the use of lurasidone for 13- to 17-year-olds who have bipolar disorder and experience a depressive episode — providing a new treatment option.[18]

METHODS

We use systematic review methods adapted from the *Cochrane Collaboration* and *Evidence-Based Mental Health*. We build quality assessment into our inclusion criteria to ensure that we report on the best available evidence — requiring that intervention studies use randomized controlled trial (RCT) methods and also meet additional quality indicators. For this review, we searched for RCTs on interventions that aimed to help youth with bipolar disorder. Table 7 outlines our database search strategy.

Table 7: Search Strategy

Sources	• Campbell, Cochrane, CINAHL, ERIC, Medline and PsycINFO
Search Terms	• Bipolar *and* treatment
Limits	• Peer-reviewed articles published in English between 2008 and 2018 • Pertaining to children aged 18 years or younger • Systematic review, meta-analysis or RCT methods used

To identify additional RCTs, we also hand-searched reference lists from relevant published systematic reviews and from previous Children's Health Policy Centre publications. Using this approach, we identified 50 studies published in the past 20 years. Two team members then independently assessed each study, applying the inclusion criteria outlined in Table 8.

Table 8: Inclusion Criteria for RCTs

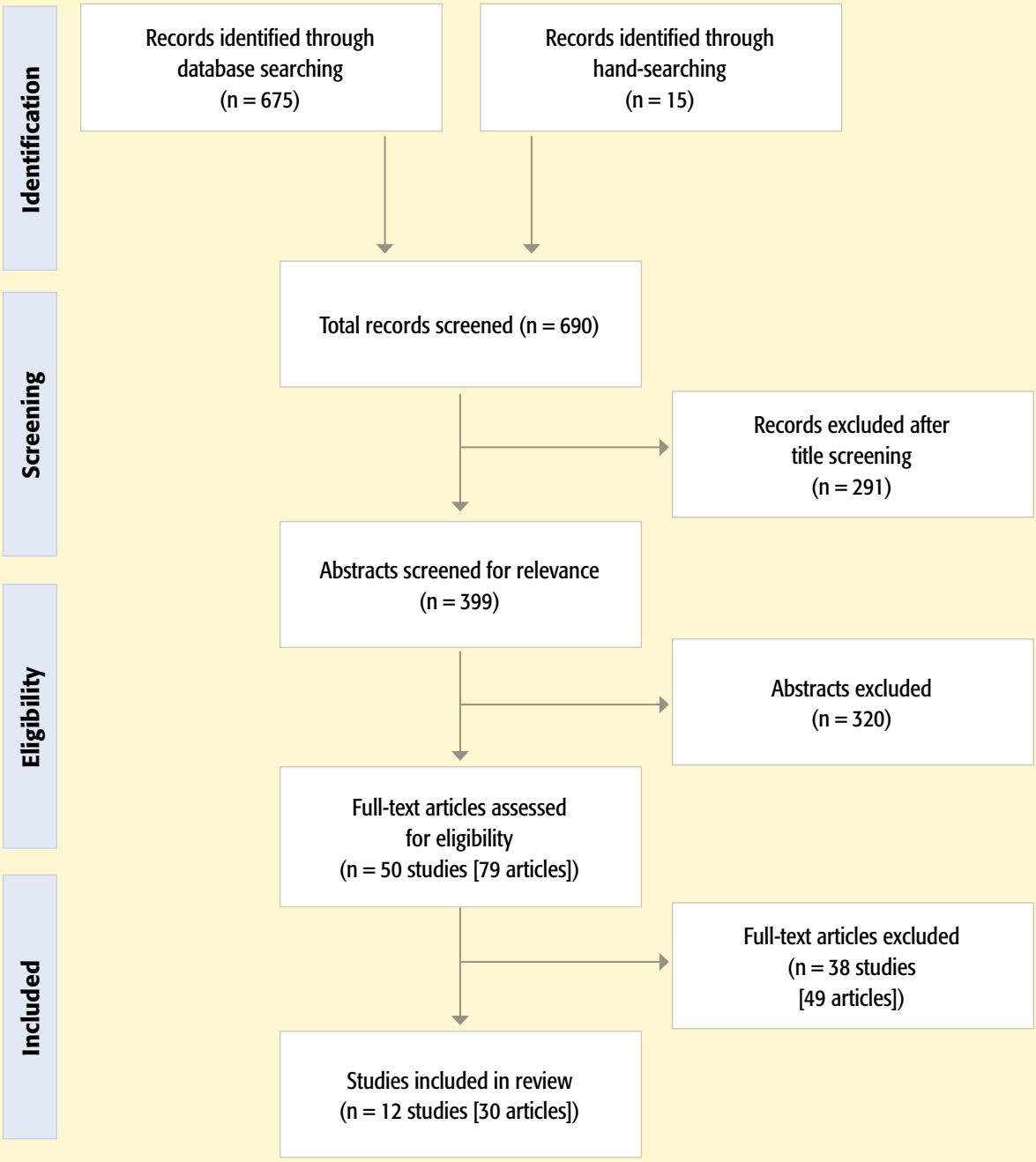
- Participants were randomly assigned to intervention and control groups
- Studies provided clear descriptions of participant characteristics, settings and interventions
- Interventions aimed to treat bipolar disorder among young people
- Interventions were evaluated in settings that were applicable to Canadian policy and practice
- At study outset, more than 50% of participants had a bipolar disorder diagnosis
- Attrition rates were 20% or less at final assessment and/or intention-to-treat analysis was used
- Child mental health indicators included manic or hypomanic symptoms
- Medication studies used double-blinding procedures and placebo controls
- Psychosocial studies had at least one outcome rater blinded to participants' group assignment
- Studies documented reliability and validity of all primary outcome measures
- Studies reported levels of statistical significance for primary outcome measures
- Side effects and adverse reactions were comprehensively assessed and reported for medications
- Studies/outcomes were excluded when there was insufficient statistical power or inappropriate analyses*

* We defined inappropriate statistical analyses as those that did not control for multiple comparisons and/or variables that might influence the outcome of interest.

Twelve RCTs met all the inclusion criteria. Figure 1, adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), depicts our search process. Data from these studies were then extracted, summarized and verified by two or more team members. Throughout our process, any differences between team members were resolved by consensus.

For more information on our research methods, please contact
Jen Barican, chpc_quarterly@sfu.ca
Children's Health Policy Centre, Faculty of Health Sciences
Simon Fraser University, Room 2435, 515 West Hastings St. Vancouver, BC V6B 5K3

Figure 1: Search Process for RCTs



RESEARCH TERMS EXPLAINED

To best help children, practitioners and policy-makers need good evidence on whether or not a given intervention works. **Randomized controlled trials** (RCTs) are the gold standard for assessing whether an intervention is effective. In RCTs, children are randomly assigned to the intervention group or to a comparison or control group. By randomizing participants — that is, giving every child an equal likelihood of being assigned to a given group — researchers can help ensure the only difference between the groups is the intervention. This process provides confidence that benefits are due to the intervention rather than to chance or other factors.

Then, to determine whether the intervention actually provides benefits to children, researchers analyze key outcomes. If an outcome is found to be **statistically significant,** it helps provide certainty the intervention was effective rather than it appearing that way due to a random error. In the studies we reviewed, researchers set a value enabling at least 95% confidence that the observed results are real.

Once an intervention has been found to have a statistically significant benefit, it is helpful to quantify the degree of difference it made, or its **effect size.** Beyond identifying that the intervention works, an effect size indicates how much of a clinically meaningful difference the intervention made in children's lives. **Cohen's *d*** was the effect size measure reported in this issue. Values can range from 0 to 2. Standard interpretations are 0.2 = small effect; 0.5 = medium effect; 0.8 = large effect.

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BC government staff can access original articles from BC's Health and Human Services Library. Articles marked with an asterisk (*) include randomized controlled trial data that was featured in our Review article.

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LINKS TO PAST ISSUES

The *Children's Mental Health Research Quarterly* Subject Index provides a detailed listing of topics covered in past issues, including links to information on specific programs.

2018 / Volume 12

4 – Helping children who have been maltreated
3 – Preventing child maltreatment
2 – Treating substance misuse in young people
1 – Preventing youth substance misuse: Programs that work in schools

2017 / Volume 11

4 – Helping children with depression
3 – Preventing childhood depression
2 – Supporting LGBTQ+ youth
1 – Helping children with ADHD

2016 / Volume 10

4 – Promoting self-regulation and preventing ADHD symptoms
3 – Helping children with anxiety
2 – Preventing anxiety for children
1 – Helping children with behaviour problems

2015 / Volume 9

4 – Promoting positive behaviour in children
3 – Intervening for young people with eating disorders
2 – Promoting healthy eating and preventing eating disorders in children
1 – Parenting without physical punishment

2014 / Volume 8

4 – Enhancing mental health in schools
3 – Kinship foster care
2 – Treating childhood obsessive-compulsive disorder
1 – Addressing parental substance misuse

2013 / Volume 7

4 – Troubling trends in prescribing for children
3 – Addressing acute mental health crises
2 – Re-examining attention problems in children
1 – Promoting healthy dating relationships

2012 / Volume 6

4 – Intervening after intimate partner violence
3 – How can foster care help vulnerable children?
2 – Treating anxiety disorders
1 – Preventing problematic anxiety

2011 / Volume 5

4 – Early child development and mental health
3 – Helping children overcome trauma
2 – Preventing prenatal alcohol exposure
1 – Nurse-Family Partnership and children's mental health

2010 / Volume 4

4 – Addressing parental depression
3 – Treating substance abuse in children and youth
2 – Preventing substance abuse in children and youth
1 – The mental health implications of childhood obesity

2009 / Volume 3

4 – Preventing suicide in children and youth
3 – Understanding and treating psychosis in young people
2 – Preventing and treating child maltreatment
1 – The economics of children's mental health

2008 / Volume 2

4 – Addressing bullying behaviour in children
3 – Diagnosing and treating childhood bipolar disorder
2 – Preventing and treating childhood depression
1 – Building children's resilience

2007 / Volume 1

4 – Addressing attention problems in children
3 – Children's emotional wellbeing
2 – Children's behavioural wellbeing
1 – Prevention of mental disorders

