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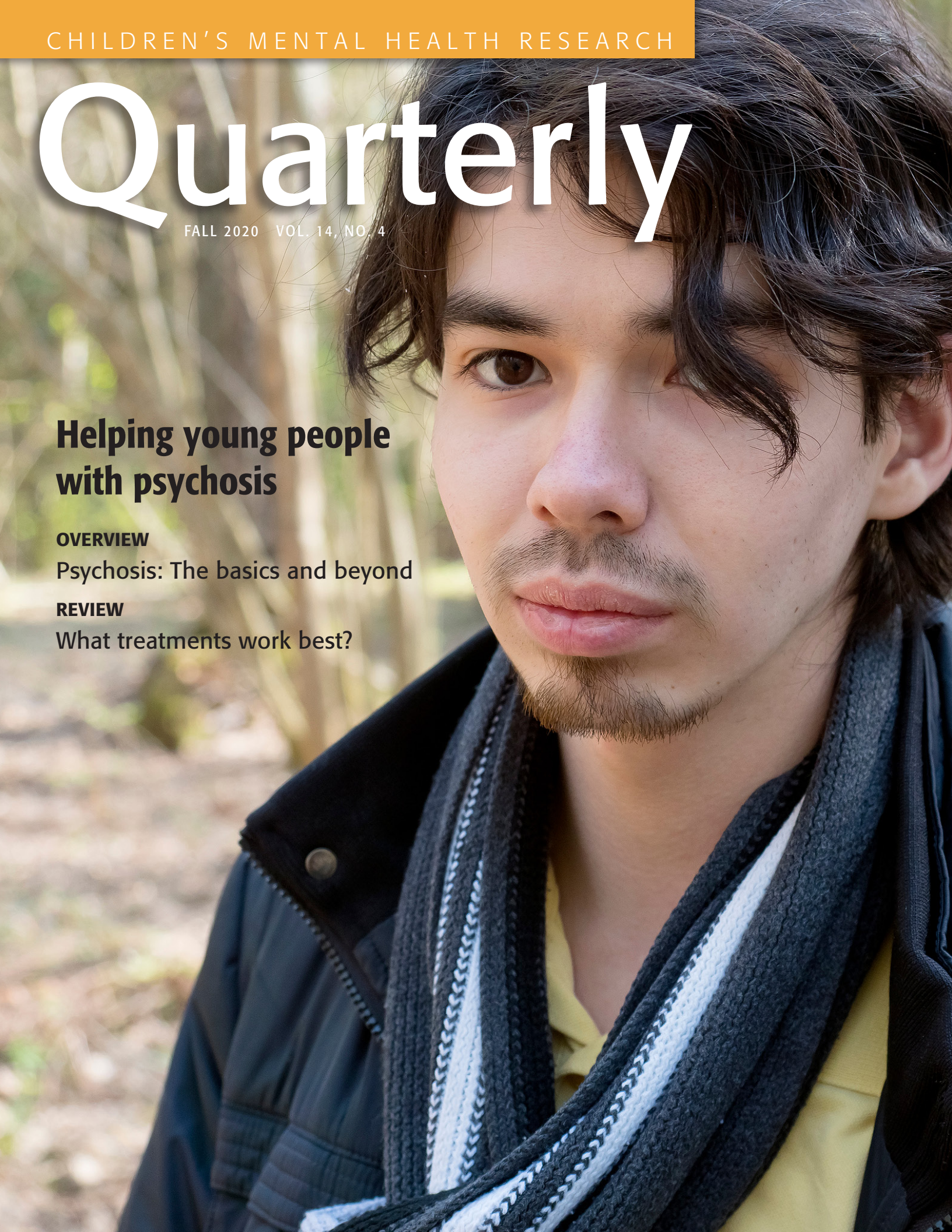

Helping young people with psychosis

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FALL

Quarterly

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Children's Health Policy Centre

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*.

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.

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This Issue

NEXT ISSUE

Helping children cope with adversity: Pathways to resilience

When childhood adversities have not been prevented, it is crucial to mitigate their impact. We review the latest research evidence on interventions designed to help.

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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Errata

In the Spring 2018 *Quarterly*, Table 2 incorrectly identified the ages of participants in an evaluation of Multidimensional Family Therapy. The correct ages are 13–18 years.

OVERVIEW

Psychosis: The basics and beyond

With effective treatments, youth with psychosis can thrive.

Psychotic symptoms are a central feature of several different mental disorders. These disorders include schizophrenia as well as delusional, brief psychotic, schizophreniform and schizoaffective disorders, all of which are classified as psychotic disorders.[1] Psychotic symptoms can also occur in some mood disorders, including depression and bipolar disorder. Substances, such as cannabis, and medical conditions, such as infections or epilepsy, can also cause psychotic symptoms.[1] Regardless of cause, ongoing psychosis is associated with a high degree of impairment — and now ranks as the 19th cause of disability worldwide.[2]

All psychotic disorders include delusions as a core feature.[1] These false beliefs are persistently maintained despite the absence of evidence to support them. Hallucinations are another feature of most psychotic disorders and involve sensations such as hearing voices or seeing objects that others do not perceive. A meta-analysis that included more than 1,500 youth with psychosis found that auditory hallucinations were the most common symptom that these young people struggled with.[3] Collectively, delusions and hallucinations are often referred to as "positive" symptoms, because they have been considered to be "an exaggeration of normal functions."[4] In contrast, the term "negative" symptoms is commonly used to refer to symptoms that represent a loss of typical functioning,[4] such as reduced expression of emotions and reduced involvement in social and academic activities. (The sidebar on page 6 provides information about using more sensitive terms to describe so-called positive and negative symptoms.) Psychosis may also include disorganized thinking that impairs communication and disorganized behaviour that interferes with daily living.

Onset of psychotic symptoms or disorders is very rare prior to the teen years.

What causes psychosis?

Sometimes the cause of psychosis can be clearly identified, for example, when episodes are a result of substance use or medical conditions. Yet many questions remain about the other causes of psychotic disorders.

Researchers have put considerable effort into identifying the causes of schizophrenia, in particular, given its lifelong consequences. Current evidence suggests that schizophrenia likely results from complex interactions occurring over time among thousands of genes and multiple environmental risk factors — none of which cause schizophrenia on their own.[5] And while genetics play a big role, it does not play the only role.[5] For example, having a first-degree relative with schizophrenia increases the risk, yet most people with this disorder do not have an affected relative.[5] Paradoxes like this have led scientists to look at environmental factors that can influence both gene expression and overall development. Prenatal exposure to infections and perinatal

complications such as hypoxia appear to increase risk.[5–6] Important risks can also occur later in a young person's development, such as heavy cannabis use.[6–7] Overall, schizophrenia likely arises as a result of atypical brain development due to multiple genetic changes and environmental risks occurring over time.[6] Recent data also suggest that schizophrenia is rare in young people — with only 0.1% of 12- to 18-year-olds meeting diagnostic criteria for this disorder.[8]

The importance of early intervention

For psychotic disorders, age of onset typically peaks at 22 years for males and 25 for females. Onset of psychotic symptoms or disorders is very rare prior to the teen years,[3] yet early symptoms sometimes emerge in adolescence.[9] Therefore, treatment services for young people with psychosis need to be readily available. Intervening early is crucial for youth with psychosis, given the strong association between duration of untreated symptoms and poorer short- and long-term outcomes.[9]

Intervening early is crucial for youth with psychosis.

Early psychosis intervention (EPI) programs were created to rapidly treat young people with psychosis. In BC, EPI programs were first established in 2000[10] and there are currently 53 such programs across the province.[11] These programs typically provide young people with comprehensive assessment, case management, medication management, support and education (including for the family), and treatment for any concurrent mental health concerns.[12–13]

EPI programs have garnered international praise as possibly "the most significant development in mental health services globally since deinstitutionalization."[9] Research evidence suggests that this enthusiasm is warranted. Specifically, a meta-analysis comparing four different EPI programs to standard care found that youth receiving EPI were more likely to have significantly reduced psychotic symptoms, less likely to relapse (32.5% vs. 51.9%), less likely to be hospitalized (28.1% vs. 42.1%), and less likely to discontinue with services (27.0% vs. 40.5%).[14]

Another important shift involves changing negative perceptions that psychosis automatically has a poor prognosis. Instead, it is being recognized that psychosis has a malleable course, a finding that may help to reduce the associated stigma for young people who have this mental health problem.[15] In the Review article that follows, we highlight effective psychosis treatments for young people that confirm these reasons for hopefulness. 👋

REVIEW

What treatments work best?


Quick access to effective treatments helps youth to flourish.

Youth with psychosis need rapid access to effective treatments. To determine which treatments are successful — and which are not — we conducted a systematic review. We built quality assessment into our inclusion criteria, requiring studies to use randomized controlled trial (RCT) evaluation methods. We then searched for RCTs that included young people and were published in the past 11 years, coinciding with when we last reviewed this topic. We also examined our previous *Quarterly* issue on psychosis to identify older studies that met our current inclusion criteria. This process enabled us to address the best RCT evidence from the past 16 years. (Please see the Methods section for more details.)

We retrieved and evaluated 42 studies. In addition to accepting double-blinded placebo-controlled medication RCTs, we also accepted head-to-head medication trials if there was previous evidence of effectiveness for either medication from placebo-controlled RCTs. (Head-to-head trials directly compare the effectiveness of two medications without using a placebo control.) For psychosocial evaluations, we accepted comparison groups including treatment as usual or active control groups (e.g., support only). Eight RCTs met our inclusion criteria.

Five of these RCTs evaluated five different medications: aripiprazole (brand name Abilify; two RCTs, including one head-to-head trial);[16–17] clozapine (brand name Clozaril);[18] lurasidone (brand name Latuda);[19] olanzapine (brand name Zyprexa; two RCTs, including one head-to-head trial);[18, 20] and quetiapine (brand name Seroquel).[17] Four of the five medication studies reported that study authors had ties to the pharmaceutical companies that manufactured the medications, including some being company employees.[16–17, 19–20] As well, lurasidone manufacturers were involved in study design, data collection and analysis, and writing of the manuscript.[19] (One older study did not report on conflicts of interest.)[18]

The remaining three RCTs assessed psychosocial interventions, namely Cognitive Remediation Therapy,[21] Computer-Assisted Cognitive Remediation,[22] and the Think Program.[23–24] No authors involved in these studies declared any conflicts of interest. (We outline another potential concern, publication bias, in the sidebar.)

Positive publication bias in intervention trials

Intervention evaluations with significant positive findings are more likely to be submitted and accepted for academic publication than those with null or negative findings — a well-known phenomenon known as publication bias.[30–32] In addition to wasting research resources when negative results do not come to light, this form of bias can mislead policy-makers and practitioners, potentially causing considerable harm to the health of children. For example, if an intervention has proven to be ineffective, or even harmful, but that result is not shared, policy-makers and practitioners may continue offering unhelpful approaches. Researchers in turn cannot include unreported negative findings, for example, when they conduct systematic reviews, which involve synthesizing findings from multiple studies — resulting in very different and possibly misleading conclusions and recommendations. These issues have led to calls for all researchers to fulfill their ethical obligation to fully share findings from their studies, whether negative or positive.

Placebo-controlled medication studies

The three RCTs using placebo controls evaluated aripiprazole,[16] lurasidone[19] and olanzapine.[20] These three RCTs evaluated responses in youth with schizophrenia for six weeks (only). Table 1 provides more details about these studies.

Table 1: Placebo-Controlled Medication Studies

Medication (brand name)	**Dose***	**Sample size**	**Ages** (years) (countries)
Aripiprazole (Abilify)[16]	10 mg/day** or 30 mg/day** over 6 weeks	302	13–17 (United States + other countries in Europe, Africa, South American, Asia + the Caribbean)
Lurasidone (Latuda)[19]	40 mg/day or 80 mg/day** over 6 weeks	327	13–17 (United States, Ukraine, Russia, Bulgaria, Romania, Colombia, Mexico, Poland, Philippines, Korea, Malaysia, Spain, France + Hungary)
Olanzapine (Zyprexa)[20]	10 mg/day** to 20 mg/day** over 6 weeks	107	13–17 (United States + Russia)

* Doses are not comparable or equivalent across different medications.
** Youth were started on a lower medication dose, which was titrated up to this final daily dose.

What did placebo-controlled medication studies find?

Aripiprazole resulted in statistically significant benefits at daily doses of both 10 mg and 30 mg — namely, higher remission rates at six weeks.[16] (Remission was defined as having no more than mild scores on eight psychosis symptoms.) Specifically, 57.7% of youth on aripiprazole achieved remission on 30 mg daily, as did 53.5% on 10 mg, compared to only 35.7% of controls.[16] Youth on either dose also had significantly fewer "positive" symptoms, such as delusions or hallucinations, and had better overall functioning and quality of life.[16] But neither dose of aripiprazole significantly reduced "negative" symptoms, such as emotional withdrawal.

Aripiprazole also led to adverse events. The most frequent problems were extrapyramidal symptoms such as changes in muscle tone and movement difficulties, drowsiness and tremors. These adverse events were worse with daily doses of 30 mg than with 10 mg.[16]

Lurasidone also led to statistically significant benefits at daily doses of both 40 mg and 80 mg at six weeks.[19] Specifically, more youth on lurasidone achieved treatment response, defined as psychotic symptoms being reduced by 20.0% or more. Overall, 65.1% had this response on the 80 mg dose, as did 63.9% on 40 mg, compared to only 42% of controls. As well, youth on lurasidone had significantly fewer psychotic symptoms, with medium effect sizes for both doses (Cohen's d = 0.48 for 80 mg and 0.51 for 40 mg). The medication also led to significantly better overall functioning, again with medium effect sizes for both doses (d = 0.45 for 80 mg and 0.49 for 40 mg). But lurasidone failed to outperform placebo for remission from psychosis by six weeks (defined as having no more than mild scores on eight psychosis symptoms).[19] Lurasidone, too, led to adverse events. The most frequent problems were nausea, restlessness, vomiting and extrapyramidal symptoms.[19]

Olanzapine also resulted in statistically significant benefits at daily doses of both 10 mg and 20 mg.[20]

Conveying respect by choosing words wisely

For practitioners and researchers, using phrases such as "positive" symptoms to describe delusions and hallucinations and "negative" symptoms to describe difficulties in engaging may seem like a helpful shortcut. But for youth with schizophrenia and their families, this phrasing may be unhelpful. Difficult and often frightening experiences with delusions and hallucinations may feel far from positive; and negatively labelling a youth's difficulties with engagement may contribute to stigma. So phrases such as "positive" and "negative" symptoms need to be replaced by more sensitive language — preferably chosen by youth themselves.

Specifically, youth on olanzapine had fewer overall psychotic symptoms and fewer "positive" symptoms, with a medium effect size for both. But olanzapine made no difference for "negative" symptoms or for treatment response rates (defined as overall symptom reductions of 30% or more by end of treatment, and as functioning being no more than "mildly ill").[20] Olanzapine also produced benefits beyond addressing psychosis, including fewer overall mental health symptoms and less physical aggression toward others.

As with aripiprazole and lurasidone, olanzapine also led to adverse events.[20] The most frequent problems were high prolactin levels (which can cause breast milk production in both sexes and impotence in males), weight gain, drowsiness, headaches, increased appetite, sedation, dizziness, high levels of alanine transaminase (which reflect changes in liver functioning), and changes in triglyceride levels (which are associated with increased risk of heart disease). Table 2 gives more details on study outcomes.

Table 2: Placebo-Controlled Medication Study Outcomes

Medication (brand name)	**Outcomes at post-test**	
Aripiprazole (Abilify)[16]	10 mg daily dose ↑ Psychosis remission NS Overall psychotic symptoms ↓ Positive psychotic symptoms* NS Negative psychotic symptoms* ↑ Overall functioning (3 of 3) ↑ Overall quality of life	30 mg daily dose ↑ Psychosis remission ↓ Overall psychotic symptoms ↓ Positive psychotic symptoms* NS Negative psychotic symptoms* ↑ Overall functioning (3 of 3) ↑ Overall quality of life
Lurasidone (Latuda)[19]	40 mg or 80 mg daily dose ↑ Treatment response rate NS Psychosis remission ↓ Overall psychotic symptoms ↑ Overall functioning	
Olanzapine (Zyprexa)[20]	10 mg to 20 mg daily NS Treatment response rate ↓ Overall psychotic symptoms ↓ Positive psychotic symptoms* NS Negative psychotic symptoms* ↓ Other mental disorder symptoms (2 of 2) ↓ Aggression (1 of 5)	

↓ or ↑ Statistically significant improvements for medication over placebo.
NS No statistically significant difference between medication and placebo.
* Please see the sidebar on page 6 for information about using more sensitive terms to describe these outcomes.

Head-to-head medication comparison trials

We also included head-to-head trials when one of the medications had already shown benefits in a double-blinded placebo-controlled RCT. We accepted two such evaluations. One compared aripiprazole and quetiapine,[17] and one compared olanzapine and clozapine.[18]

In the study comparing aripiprazole and quetiapine, participating youth had psychotic symptoms due to schizophrenia, or delusional, schizoaffective or mood disorders.[17] (Quetiapine was extended release.) Youth received either medication for 12 weeks.

In the study comparing olanzapine and clozapine, young people participating had been diagnosed with schizophrenia before age 13, and they had persistent symptoms and impairment despite being tried on at least two other antipsychotic medications.[18] Young people received either olanzapine or clozapine for eight weeks. All participants also received

Expanding the psychosocial treatment options for youth with psychosis is particularly important.

up to four hours per day of specialized education, recreational and occupational therapy, and nursing care.[18] Table 3 gives more details about these studies.

Table 3: Head-to-Head Medication Comparison Studies

Medication (brand name)	**Dose***	**Sample size**	**Ages** (years) (countries)
Aripiprazole (Abilify) vs.	20 mg/day** over 12 weeks	113	12–17 (Denmark)
Quetiapine (Seroquel)[17]	600 mg/day** over 12 weeks		
Clozapine (Clozaril) vs.	150–500 mg/day over 8 weeks	25	7–16 (United States)
Olanzapine (Zyprexa)[18]	5–20 mg/day over 8 weeks		

* Youth were started on a lower medication dose, which was titrated up to the reported final daily dose; doses are not comparable or equivalent across different medications.
** Doses could be raised to 30 mg and 800 mg for aripiprazole and quetiapine, respectively, if clinically indicated.

What did head-to-head medication comparison studies find?

The study comparing aripiprazole and quetiapine found that both medications led to significant reductions in "positive" symptoms, with no meaningful difference between the medications.[17] (Positive symptoms assessed included delusions and hallucinations.)

The two medications did yield significant differences in adverse events. Youth on aripiprazole experienced extrapyramidal symptoms, restlessness, reduced sleep, increased salivation, nausea, photosensitivity, weight loss and cognitive difficulties at higher rates than youth on quetiapine. In contrast, youth on quetiapine experienced insulin resistance, difficulties concentrating, increased sleep, emotional indifference, reduced salivation, nosebleeds, infections and weight gain (6.4 kg vs. 1.8 kg) at higher rates than youth on aripiprazole.[17] In addition, more than two-thirds of youth on both medications experienced tremor, dizziness, depression, tension and memory difficulties. Notably, 12.1% of youth discontinued aripiprazole due to adverse events, versus only 5.5% for quetiapine.[17]

Antipsychotics are a mainstay in treating psychosis in young people.

The other head-to-head trial found one outcome favouring clozapine over olanzapine.[18] After eight weeks, clozapine produced significantly greater reductions in "negative" symptoms than olanzapine (Cohen's $d = 0.8$). Still, both medications led to benefits regarding symptoms and functioning compared with no medication. Both resulted in fewer overall psychotic symptoms, fewer negative symptoms and fewer symptoms of mental disorders generally, with all but one outcome having a large effect size. However, only clozapine reduced "positive" symptoms and improved overall functioning with large effect sizes after eight weeks (Cohen's $d = 1.0$ and 1.4, respectively).[18]

Regarding adverse events, both clozapine and olanzapine resulted in marked increases in weight (4 kg in eight weeks) and body mass index.[18] But clozapine led to significantly more adverse events overall than olanzapine, including hypertension and higher resting heart rates, both of which can increase risk for cardiovascular disease. Study authors also tracked side effects for 18 of the 25 original participants for two years after the trial ended. By that time, eight additional youth were prescribed clozapine because they had not improved on olanzapine. At the two-year point, clozapine's profile was particularly concerning, with one participant having extreme weight gain, one developing seizures needing anticonvulsant treatment, and

six developing high cholesterol and/or high triglyceride levels, both of which increase risk for cardiovascular disease. Table 4 gives more details on study outcomes.

Table 4: Head-to-Head Medication Comparison Study Outcomes

Medication (brand name)	Outcomes at post-test	
	Favours medication over comparison	**Improvements at final assessment**
Aripiprazole (Abilify) vs.	None	↓ Positive psychotic symptoms*
Quetiapine (Seroquel)[17]	None	↓ Positive psychotic symptoms*
Clozapine (Clozaril) vs.	↓ Negative psychotic symptoms*	↓ Overall psychotic symptoms ↓ Positive psychotic symptoms* ↓ Negative psychotic symptoms* ↑ Overall functioning ↓ Overall mental disorder symptoms NS Depressive symptoms NS Manic symptoms NS Anxiety symptoms
Olanzapine (Zyprexa)[18]	None	↓ Overall psychotic symptoms NS Positive psychotic symptoms* ↓ Negative psychotic symptoms* NS Overall functioning ↓ Overall mental disorder symptoms NS Depressive symptoms NS Manic symptoms NS Anxiety symptoms

↓ or ↑ Statistically significant improvements.
* Please see the sidebar on page 6 for information about using more sensitive terms to describe these outcomes.
NS No statistically significant difference.

Including psychosocial interventions for youth with psychosis

All three of the psychosocial interventions were designed to address common concerns for youth with psychosis. These concerns included daily life stressors and cognitive challenges associated with their mental health condition.

Cognitive Remediation Therapy aimed to improve cognitive functioning for youth with schizophrenia.[21] The program, delivered in 40 hours over 12 weeks, was designed to improve memory, planning and problem-solving.[21] All study participants were experiencing cognitive and social challenges and had been on antipsychotic medication for at least a month. Controls received treatment as usual.

Some youth with psychosis may benefit from psychosocial interventions.

Computer-Assisted Cognitive Remediation similarly aimed to improve cognitive functioning, primarily for youth with a psychotic disorder but also for youth assessed as being at high risk for psychosis.[22] The program, delivered in 12 hours over eight weeks, was designed to improve attention, memory and logical thinking. All study participants were experiencing challenges, such as memory and attention difficulties, and most (56.3%) were taking antipsychotic medications. Control youth participated in computer games requiring attention and motor skills.[22]

The third intervention, the Think Program, aimed to help young people manage difficulties with daily living due to psychosis and to prevent relapses, by also involving their parents.[23] The 20-hour program was delivered over nine months. It included three individual sessions for youth and parents, provided separately, as well as 12 group sessions for youth and parents, also provided separately. All youth study participants were

living with a parent.[23–24] Almost all youth (96.4%) were also taking antipsychotic medications.[23] Control youth and parents received support only. Table 5 gives more details about these three interventions.

Table 5: Psychosocial Treatment Studies

Intervention	**Components**	**Sample size**	**Ages** (years) (countries)
Cognitive Remediation Therapy[21]	Youth completed memory, planning + problem-solving exercises during 40 individual sessions over 12 weeks	40	14–22 (England)
Computer-Assisted Cognitive Remediation[22]	Youth completed memory, attention + logical thinking exercises during 16 individual sessions over 8 weeks	32	13–18 (Switzerland)
Think Program[23–24]	Youth + parents separately completed psycho-educational program focused on problem-solving skills during 3 individual sessions + 12 group sessions over 9 months	55	14–18 (Spain)

Psychosocial treatments produced limited benefits

At three-month follow-up, youth who had received Cognitive Remediation Therapy displayed significantly better cognitive flexibility than controls, with a medium effect size (Cohen's $d = 0.55$).[21] But there were no differences between the groups for any other outcomes, including overall cognitive functioning, memory, planning, social functioning, self-esteem, quality of life or general mental disorder symptoms.[21]

By post-test, youth who had completed Computer-Assisted Cognitive Remediation outperformed controls on one outcome — visual-spatial skills — with a medium effect size (Cohen's $d = 0.62$).[22] But there were no significant group differences for any other outcomes, including memory, language abilities, attention, psychosocial functioning or psychotic symptoms.[22]

At two-year follow-up, youth who had participated in the Think Program showed one benefit: significantly fewer emergency room visits for mental health concerns compared to controls (13% vs. 50%, respectively).[24] Yet there were no significant group differences on any other outcomes, which consisted of psychotic symptoms, psychotic diagnoses, hospitalizations (including time in the community until hospitalization was

Family support is vital for youth experiencing psychosis.

needed, number of admissions and total days in hospital) and overall functioning.[24] Table 6 gives more details on study outcomes.

Table 6: Psychosocial Treatment Study Outcomes

Intervention	Follow-up	Outcomes
Cognitive Remediation Therapy[21]	3 months	NS Mental disorder symptoms NS Quality of life NS Cognitive functioning ↑ Cognitive flexibility NS Memory NS Planning NS Social functioning NS Self-esteem
Computer-Assisted Cognitive Remediation[22]	None	NS Overall psychotic symptoms NS Positive psychotic symptoms* NS Negative psychotic symptoms* NS General psychotic symptoms ↑ Visual-spatial skills NS Memory NS Language abilities NS Attention NS Psychosocial functioning (2 of 2)
Think Program[23–24]	2 years	NS Overall psychotic symptoms NS Positive psychotic symptoms* NS Negative psychotic symptoms* NS General psychotic symptoms NS Psychotic disorder diagnoses NS Number of mental health hospitalizations NS Number of days in hospital NS Time until hospitalized ↓ Emergency room visits for mental health concerns NS Overall functioning

NS No statistically significant difference between treatment and control participants.
↓ or ↑ Statistically significant improvements for intervention over control participants.
* Please see the sidebar on page 6 for information about using more sensitive terms to describe these outcomes.

Recapping treatment choices

Regarding medications for treating youth with psychosis, we found two RCTs for both aripiprazole and olanzapine, each suggesting benefits, with aripiprazole leading to greater remission rates. Yet both medications also led to adverse events that require close monitoring. The other antipsychotics in our review also led to benefits, but these were only shown in one RCT, and all came with adverse events.

Our review of medications has two concerning implications that should be addressed in future research. First, no medication studies in our review were conducted at arm's length from the drug manufacturers. Future studies need to be conducted independently, particularly given the safety profiles of antipsychotics. Second, we did not find RCT evidence that met our criteria on risperidone (brand name Risperidal), which is commonly prescribed for young people.[25] Other researchers have raised concerns about the poor quality of trials on risperidone (and other antipsychotics).[26] It is therefore important that new trials be conducted to expand the evidence on effective medications for treating young people who have psychosis.

Regarding psychosocial interventions, Cognitive Remediation Therapy and Computer-Assisted Cognitive Remediation both improved selected cognitive skills, and the Think Program reduced emergency room visits for mental health concerns. These approaches may be helpful when used along with antipsychotic medications.

Yet there are psychosocial research implications as well. Most importantly, new trials are needed to expand the treatment options. For example, a form of cognitive-behavioural therapy (CBT) shows promise with first-episode psychosis, according to a recent pilot study in youth aged 14 to 18 years.[27] This form of CBT involved setting individual goals and helping young people achieve them. Although too few youth were recruited to definitively assess the impact, initial findings suggested that CBT may reduce psychotic symptoms.[27] Further evaluation of CBT is therefore warranted.[28] Expanding the psychosocial treatment options for youth with psychosis is particularly important given the severe side effects of antipsychotic medications.

Implications for practice and policy

The results of this systematic review suggest three implications for practice and policy.

- *Ensure careful assessment and diagnosis.* Some causes of psychosis, such as substance use, are reversible. Some causes, such as seizures or infections, are also treatable. So a first step is always to ascertain what is causing the presenting problem. Diagnosis can then guide treatment planning, for example, considering whether longer-term antipsychotic medications are needed, as in the case of schizophrenia. After the diagnosis has been established, ongoing monitoring is also crucial — to assess a youth's symptoms, functioning and response to treatment, including any adverse effects.
- *Use antipsychotic medications carefully.* Antipsychotics are a mainstay in treating psychosis in young people — both short and long term. Aripiprazole and olanzapine stood out in this review, with two RCTs for each medication showing benefits in young people. Yet adverse events were common and severe, so both choice of medication and dosing need to be carefully monitored to ensure that benefits outweigh harms. Canadian guidelines address monitoring for aripiprazole and olanzapine as well as some of the other medications included in this review. These guidelines need to be closely followed for any youth who is prescribed antipsychotics.
- *Offer psychosocial interventions as well.* Some youth with psychosis will have challenges that antipsychotics do not address and may benefit from psychosocial interventions. The three psychosocial programs we identified — Cognitive Remediation Therapy, Computer-Assisted Cognitive Remediation and the Think Program — showed modest benefits. However, as noted in the Overview, a meta-analysis of early psychosis intervention (EPI) programs found that they produced very important benefits, including reduced hospitalizations and psychotic symptoms. EPI programs typically included a range of psychosocial interventions, such as CBT, social skills training and family interventions.[14] Therefore EPI programs should be offered to all youth with psychosis. As well, new research would help to better understand the differential effects of the components of EPI programs — leading to more and better treatment options in future.

Early interventions can help young people with psychosis return to healthy development and functioning.

Psychosis can cause great distress, concerning symptoms and substantial costs for young people and their families and communities — including the costs of lost human potential when healthy development is interrupted.[29] Research shows that interventions can mitigate the distress and symptoms, particularly if young people receive these early in the course of the disorder. Antipsychotic medications are a mainstay of treatment, albeit with careful monitoring given their side effects, as are EPI programs. Meanwhile, new psychosocial treatments are also emerging. Early interventions can help young people with psychosis return to healthy development and functioning — and return to flourishing.

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 research evidence — requiring that intervention studies use randomized controlled trials (RCTs) and meet additional quality indicators. For this review, we searched for RCTs on effective interventions for treating psychosis. Table 7 outlines our database search strategy.

Table 7: Search Strategy

Sources	• CINAHL, ERIC, Medline and PsycINFO
Search Terms	• Schizophrenia or psychosis *and* prevention, intervention or treatment
Limits	• Peer-reviewed articles published in English between 2009 and 2020 • Pertaining to children aged 18 years or younger • RCT methods used

To identify additional RCTs, we also hand-searched the Web of Science database, reference lists from relevant published systematic reviews and previous issues of the *Quarterly*. Using this approach, we identified 42 studies. Two team members then independently assessed each study, applying the inclusion criteria outlined in Table 8.

Table 8: Inclusion Criteria for RCTs

- Participants had mean age of 18 years or younger
- Studies provided clear descriptions of participant characteristics, settings and interventions
- Interventions were evaluated in settings that were applicable to Canadian policy and practice
- Interventions aimed to treat psychosis
- At study outset, most participants met diagnostic criteria for a psychotic disorder
- Attrition rates were 20% or less at final assessment and/or intention-to-treat analysis was used
- Child outcome indicators included psychotic symptom and/or diagnostic outcomes
- Studies reported levels of statistical significance for primary outcome measures
- Studies were excluded when there was insufficient statistical power or inappropriate analysis*

Psychosocial Treatment Studies

- Participants were randomly assigned to intervention and comparison groups (i.e., active control or treatment-as-usual) at study outset
- At least one outcome rater was blinded to participants' group assignment

Medication Studies

- Participants were randomly assigned to intervention and placebo control groups at study outset; head-to-head comparison trials were only accepted if at least one medication was already established as being effective in a placebo-controlled RCT with young people
- Double-blinding procedures were used

* We defined inappropriate analysis as not controlling for multiple comparisons or variables that might influence outcomes.

Eight RCTs met all the inclusion criteria. Figure 1 depicts our search process, adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses. 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

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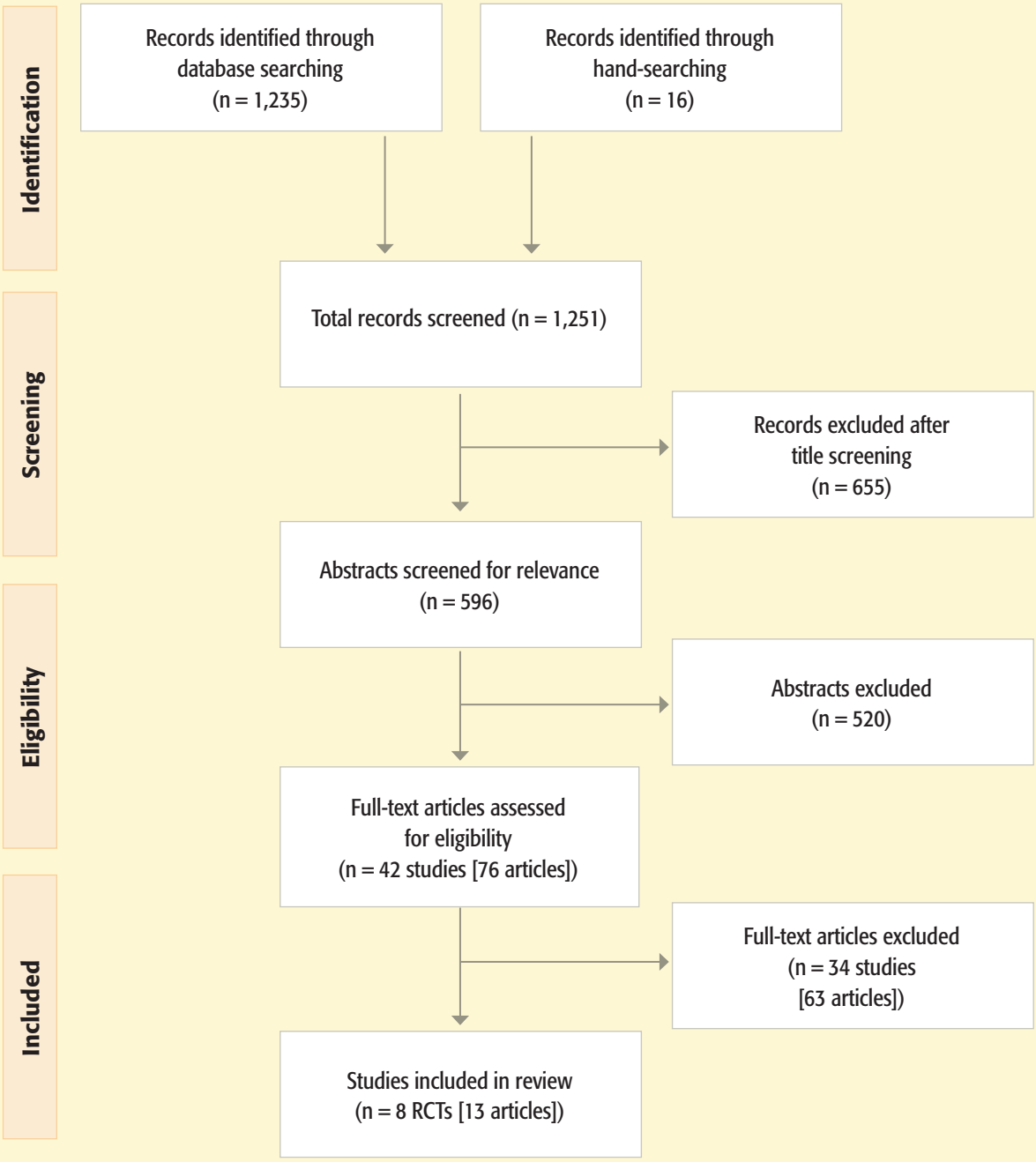
Figure 1: Search Process for RCTs



RESEARCH TERMS EXPLAINED

Practitioners and policy-makers need good evidence about whether a given intervention works to help children. **Randomized controlled trials** (RCTs) are the gold standard for assessing whether an intervention is effective. In RCTs, children, youth or families are randomly assigned to the intervention group or to a comparison or control group. By randomizing participants — that is, by giving every young person 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.

The highest standard for assessing medication effectiveness and safety involves RCTs designed so that control youth receive a placebo and so that youth and assessors are blinded regarding who is in the intervention and who is in the control groups. All medication RCTs were also **double-blinded** so neither youth nor researchers knew which group young people were assigned to — whether it was a head-to-head medication trial or a placebo control trial. This approach is typical for medication studies; it helps to ensure that beliefs about the potential effectiveness of the intervention do not influence outcomes.

To determine whether the intervention actually provides benefits, researchers analyze relevant outcomes. If an outcome is found to be **statistically significant,** it helps provide certainty the intervention was effective rather than results appearing that way due to chance. In the studies we reviewed, researchers used the typical convention of having at least 95% confidence that the observed results actually reflected the program's real impact.

As well, several studies included in this issue also calculated **effect sizes,** which described the degree of clinically meaningful difference the intervention made in young people's lives. The studies reported on **Cohen's *d***, which can range from 0 to 2. Standard interpretations are 0.2 = small effect; 0.5 = medium effect; and 0.8 = large effect. 🖐

Effect sizes describe the degree of clinically meaningful difference the intervention made in young people's lives.

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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.

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