CHILDREN'S MENTAL HEALTH RESEARCH

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Troubling trends in prescribing for children

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Children's Health Policy Centre

ABOUT THE CHILDREN'S HEALTH POLICY CENTRE

As an interdisciplinary research group in the Faculty of Health Sciences at Simon Fraser University, we aim to connect research and policy to improve children's mental health. To learn more about our work, please see childhealthpolicy.ca.

ABOUT THE *QUARTERLY*

In the *Quarterly*, we present summaries of the best available research evidence on children's mental health topics, using systematic review and other methods adapted from the *Cochrane Collaboration* and *Evidence-Based Mental Health*. The BC Ministry of Children and Family Development funds the *Quarterly*.

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This Issue

NEXT ISSUE

Helping children when parents misuse substances

Many children grow up in families where parents struggle with substance use disorders. We review interventions to help these children.

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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Assessing the risks of off-label prescribing

Although some drugs prescribed off-label are done so appropriately, most of the off-label prescribing in Canada doesn't have a scientific basis.

— A researcher[1]

In Canada, before any medication is approved for sale, Health Canada's Therapeutic Products Directorate must review its safety and effectiveness.[2] Scientists at this agency review data provided by the drug's manufacturer. If benefits are found to outweigh risks, and if these risks can be reasonably mitigated, then the manufacturer is permitted to sell the drug.[2]

However, once a drug is approved for sale, physicians are not restricted as to *how* they prescribe it. Instead, they may prescribe for both conditions and populations for which the drug has not been approved. For example, a physician may prescribe a drug to a child or youth even though the drug is approved for use only in adults. This practice is known as "off-label" prescribing.[3]

Physicians who adhered to "evidence-based practice" principles — defined as identifying research evidence as "the best source" for informing clinical decision-making — were significantly less likely to prescribe off label.

Frequency of off-label psychiatric prescribing

Recent population-based studies have found that young people frequently receive off-label psychiatric prescriptions. For example, a nationwide study of German children documented that more than a third of all psychiatric drugs were prescribed off label, with antipsychotic and antidepressant prescriptions of this type being particularly high.[4] Similarly, a nationwide study of Icelandic children documented that a quarter of all psychiatric drugs were prescribed off label, with off-label hypnotics/sedative, antipsychotic and antidepressant prescribing being particularly common.[5]

Off-label psychiatric prescribing for children and youth is also common in North America. One US study tracked outpatient antidepressant prescriptions for six- to 18-year-olds and found that 91% were off-label.[6] These off-label uses included prescribing antidepressants that were not approved for pediatric populations and prescribing them for non-indicated conditions, such as attention-deficit/hyperactivity disorder (ADHD).[6] Two Canadian studies, examined in detail in the upcoming Review article, also found high rates of off-label antipsychotic prescribing.[7, 8]

The usual safety and efficacy data, required for medications to receive "on-label" approval, are often lacking for off-label uses.

What's the problem with off-label psychiatric prescribing?

There are several concerns about off-label psychiatric prescribing for children and youth. Foremost, often limited information exists about potential harms. These harms may include side effects such as negative consequences for growth and development, as well as adverse health events such as the development of cardiovascular problems associated with certain antipsychotics in young people.[9, 10] Information is limited because the usual safety and efficacy data, required for medications to receive "on-label" approval, are often lacking for off-label uses.[3]

This is not the only concern. When physicians are willing to prescribe off label, drug companies may have little motivation to invest in costly clinical trials with children and youth. Consequently, off-label prescribing may inadvertently undermine the goal of conducting rigorous safety and efficacy studies in children and youth.

Off-label prescribing can also add financial costs. For example, when physicians prescribe newer and more expensive off-label drugs over older and less costly alternatives, health care costs increase — for individuals and for society collectively.[3] Finally, off-label prescribing can erode public trust in physicians and the health care system — because parents receiving a prescription for their child expect that the drug's safety and efficacy have been comprehensively evaluated, but this is not assured for off-label uses.[3]

Making careful clinical decisions

Given the concerns with off-label prescribing, why does this practice persist? One crucial reason is that very few psychiatric medications have Health Canada approval for pediatric use. Schizophrenia and bipolar disorder are two disorders that illustrate why physicians may have to resort to off-label prescribing. Physicians have long needed antipsychotic medications to treat psychosis and mania, given the severe and disabling symptoms associated with these two disorders. Yet only one newer antipsychotic (aripiprazole) has been approved by Health Canada for pediatric use, and this approval was only granted in 2009.[13] Consequently, before 2009, all prescribing of newer antipsychotics for Canadian young people was effectively off-label. Even now, many newer antipsychotics have yet to receive regulatory approval.

Fortunately, there is another source of information besides Health Canada to guide clinical decision-making. Physicians can turn to the best available research evidence — randomized controlled trials published in peer-reviewed journals — to guide their practice while waiting for Health Canada approvals. For example, many physicians would feel compelled — clinically and ethically — to prescribe off label newer antipsychotics for youth with schizophrenia and bipolar disorder, given the gravity of these disorders. In these situations, physicians can use research evidence to help guide their selection of a particular antipsychotic.

The need for enforcement

In 2009, the US government issued what was then its largest-ever criminal fine in a health care case.[11] The pharmaceutical conglomerate Eli Lilly agreed to pay more than $1.4 billion for promoting its antipsychotic, olanzapine (sold under the trademark name Zyprexa), for uses not approved by the Food and Drug Administration.[11] The company's marketing campaign aimed at doctors — "Viva Zyprexa" — was specifically found to promote the use of this drug in children and adolescents, despite its lack of any pediatric approval.[12] As part of the settlement, Eli Lilly had to comply with close ongoing monitoring of its marketing and sales practices.[11] While this case illustrates the potential for deliberate abuses of the drug approval process, it also illustrates the potential for regulatory agencies to enforce their guidelines and rectify abuses by pharmaceutical companies.

What makes physicians less likely to prescribe off label?

At times, however, neither regulatory approvals *nor* the research evidence guides prescribing practices. To better understand why this occurs, Canadian researchers have studied the characteristics of those physicians who were more likely to prescribe off label. They found only one characteristic that mattered. Physicians who adhered to "evidence-based practice" principles — defined as identifying research evidence as "the best source" for informing clinical decision-making — were significantly less likely to prescribe off label, *especially* when the research evidence was also weak.[14]

Improving safety

Several remedies can mitigate the potential harms of off-label psychiatric prescribing for children and youth. More high-quality pediatric medication trials are a crucial first step — to determine efficacy and safety of specific medications for young people. As part of this, governments can mandate that pharmaceutical companies study medications in young people as part of the approval process.

For example, the US Congress and the European Parliament passed legislation requiring manufacturers who anticipate their medications being used in pediatric populations to conduct studies and submit results to regulatory bodies in advance, in return for six-month extensions of market exclusivity.[15] These incentives resulted in more pediatric drug studies and more attention to delineating pediatric indications and dosing.[15] However, when this approach was tried in Canada, its success was quite limited. The relatively small size of the Canadian market likely played a role in few manufacturers submitting the necessary data for Canadian pediatric indications and dosing.[15] Consequently, additional strategies may be needed, such as international harmonization of laws promoting pediatric research.[15]

Monitoring is another way to try to improve safety. With this goal in mind, the World Health Organization (WHO) promotes the reporting of medication-related problems among the 139 countries participating in its Programme for International Drug Monitoring.[16] Member countries (including Canada) forward data from their national drug monitoring centres to the organization.[10] The WHO then compiles and disseminates information on the risk-benefit profiles of all medicines, including psychiatric medications used in young people.[16]

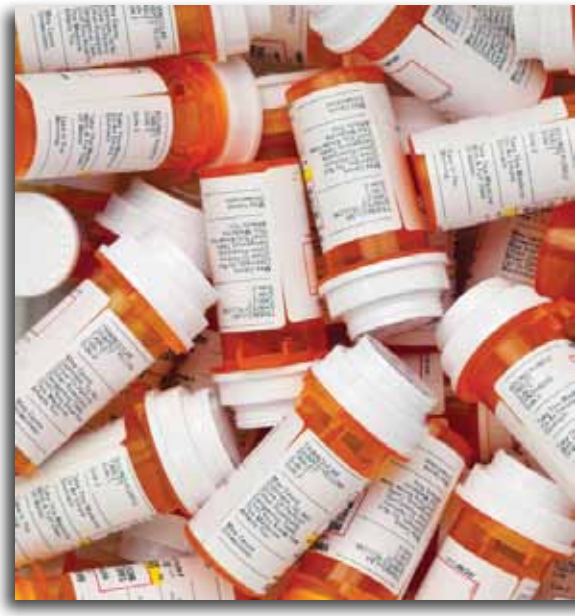
Addressing the concerns associated with off-label psychiatric prescribing for children and youth will likely require multiple approaches — including new legislation and new studies. Meanwhile, physicians will have to continue to rely on high-quality research evidence and on ongoing monitoring programs to ensure that the medications they prescribe for children and youth are both safe and effective.

Addressing the concerns associated with off-label psychiatric prescribing for children and youth will likely require multiple approaches — including new legislation and new studies.

Problematic patterns in antipsychotic prescribing

Of the approximately 800,000 Canadian children and youth who experience mental disorders at any given time, many will be prescribed psychiatric medications, or psychotropics.[17] But how many of these prescriptions are *appropriate* — regarding either "on-label" uses approved by Health Canada or uses supported by the best available research evidence?

To answer these questions, we identified: 1) studies on psychotropics prescribed to Canadian children and youth, including the psychiatric conditions these medications were prescribed for; 2) Health Canada approvals for the most commonly prescribed psychotropics identified in these studies; and 3) the best available research evidence on these psychotropics and their uses in children and youth.



Both studies uncovered striking increases in the number of antipsychotic prescriptions written and dispensed for children and youth.

Identifying the evidence

First, we searched for studies on all psychotropics being prescribed for young people in Canada. Three studies met our inclusion criteria: one from BC[8] and two from Manitoba.[7, 18] All three assessed antipsychotics only. Because there was considerable overlap between the two Manitoba studies, we selected the more recent, which was not only more current but also more comprehensive.

Next, we conducted searches of Health Canada's website to determine the approval status for the antipsychotics identified in these two studies. We limited our searches to "second-generation" or "newer" antipsychotics, because these constituted the vast majority of antipsychotic prescriptions written for children and youth in recent years in BC and Manitoba.[7, 8] (The sidebar provides more information on these medications.)

Finally, we identified the best available research evidence on newer antipsychotics in children and youth. More specifically, for these medications, we searched for published double-blind randomized controlled trials (RCTs) showing positive outcomes related to a specific diagnosis in children or youth. We also required that there be at least two RCTs, one with placebo controls, meeting these criteria to classify a medication as being "supported by the research evidence." (Our Methods provide further information on these three searches.)

A different kind of generation gap

Antipsychotics have sometimes been described as either first- or second-generation. The first-generation antipsychotics — also known as "typical" or "older" antipsychotics — were introduced in the 1950s. Since their arrival on the market, they have been associated with a host of disturbing side effects, particularly neurological problems. When second-generation antipsychotics — also known as "atypical" or "newer" antipsychotics — became available in Canada in the 1990s, they were heralded as being equally effective but without the same problematic side effects.[18] Now, however, troubling side effects for newer antipsychotics are also emerging — including significant weight gain, altered blood glucose and lipids, and high blood pressure.[19] Consequently, many researchers now suggest carefully weighing the risks and benefits for all antipsychotics before prescribing, based on their specific efficacy and side effect profiles.[20]

Antipsychotic prescribing in BC and Manitoba

The BC and Manitoba studies both tracked all antipsychotic prescriptions written and dispensed for children and youth (birth through 18 years) using comprehensive provincial health databases.[7, 8] BC researchers tracked these prescriptions for 15 years (1996–2011), and Manitoba researchers tracked them for 10 years (1998–2008). Both studies included all outpatient prescriptions; the Manitoba study also included inpatient prescriptions.

Both studies uncovered striking increases in the number of antipsychotic prescriptions written and dispensed for children and youth. In BC, these prescriptions increased nearly fourfold between 1996 and 2011.[8] Similarly in Manitoba, these prescriptions increased three- to fourfold between 1999 and 2008.[7]

Notably, most of these prescribing increases were accounted for by newer antipsychotics, with these comprising approximately 95% of all antipsychotic prescriptions written for children and youth by the end of both studies.[7, 8] Three particular newer antipsychotics — risperidone, quetiapine and olanzapine — were the ones most frequently prescribed in both studies.[7, 8] Other second-generation antipsychotics tracked were aripiprazole, clozapine, paliperidone and ziprasidone. The sidebar provides the Canadian trademark names for these seven antipsychotics.

Both studies also linked antipsychotic prescribing with diagnoses. In the final year of each study (the only year reported here, to reflect the most current practices), antipsychotics were most frequently prescribed for:

- Depression, attention-deficit/hyperactivity disorder (ADHD) and anxiety in BC children and youth[8]
- ADHD, conduct disorders (including oppositional defiant disorder or ODD) and tic disorders in Manitoba children and youth[7]

Table 1 outlines further findings from the two studies.

A medication by any other name

The second-generation antipsychotics featured in the Review article are all identified by their generic names. Each one is also sold under a trademark name. The following table identifies the Canadian trademark names associated with each generic formulation.[21]

Generic Name	Trademark Name
aripiprazole	Abilify
clozapine	Clozaril
olanzapine	Zyprexa
paliperidone	Invega
quetiapine	Seroquel
risperidone	Risperidal
ziprasidone	Zeldox

Table 1: Antipsychotic Prescribing in BC and Manitoba

	BC	Manitoba
Study years	1996 – 2011 (15 years)	1998 – 2008 (10 years)
Participant ages	Birth through 18 years	Birth through 18 years
Data sources	PharmaNet database (all outpatient prescriptions)	Drug Program Information Network (all outpatient & inpatient prescriptions)
Antipsychotics most frequently prescribed*	• Risperidone (48.0%) • Quetiapine (36.2%) • Olanzapine (5.9%)	• Risperidone (63.6%) • Quetiapine (20.6%) • Olanzapine (10.2%)
Diagnoses most frequently linked to antipsychotic prescribing*	• Depression • Attention-deficit/hyperactivity disorder • Anxiety disorders	• Attention-deficit/hyperactivity disorder • Conduct & oppositional defiant disorders • Tic disorders
Increases in antipsychotic prescribing**	3.8-fold (both males & females)	3.2- & 4.1-fold (females & males, respectively)

* Prescriptions and diagnoses are only listed for the final year of the study to reflect most current practices.
** Data reflect increases over the duration of the studies in both second- and first-generation antipsychotic prescriptions; however, the latter constituted only a tiny minority (under 5%) of prescriptions in the final study years.

Which newer antipsychotics have regulatory approval?

We sought to determine whether the prescribing patterns found in BC and Manitoba were consistent with regulatory approval for newer antipsychotics sold in Canada. Because approval status was identified only in the Manitoba study, and because approvals changed after this study finished, we independently identified the current approval status for the seven second-generation antipsychotics tracked in the studies. We found that only aripiprazole is approved for pediatric use (granted in 2009). Furthermore, aripiprazole is approved only for older youth with one of two conditions: bipolar disorder (13- to 17-year-olds) or schizophrenia (15- to 17-year-olds). Health Canada currently labels all other newer antipsychotics as lacking established safety and efficacy for anyone under age 18 years.[2] (Please see our Methods for more details on our approaches for determining Health Canada approval.)

What the research evidence suggests

Beyond the question of off-label use, were the prescribing patterns in BC and Manitoba consistent with the best available research evidence on newer antipsychotics? Because both studies provided limited information about this question, we conducted a comprehensive search to identify the best available research evidence on the effectiveness of these antipsychotics in children and youth. (Again, please see our Methods and the sidebar for details on our approaches.)

We found high-quality research evidence supporting the use of four newer antipsychotics for treating specific mental disorders or symptoms in children or youth. Aripiprazole reduced challenging secondary behaviours associated with autism spectrum disorder (e.g., hyperactivity and repetitive behaviours) in children and youth.[22, 23] It also reduced core symptoms of bipolar disorder (i.e., mania) in youth.[24, 25] Olanzapine reduced core symptoms of schizophrenia (i.e., psychosis) in youth.[26–28] Quetiapine reduced core symptoms of bipolar disorder[29, 30] and conduct disorder (i.e., aggressive behaviour) in youth.[31, 32] Finally, risperidone reduced challenging secondary behaviours associated with autism spectrum disorder in children and youth.[33–37] It also reduced core symptoms of bipolar disorder and schizophrenia in youth as well as core symptoms of conduct, oppositional defiant and tic disorders in children and youth.[27, 28, 38–46]

Our standards for defining high-quality research

The goal of the *Quarterly* is to provide summaries of high-quality research evidence on children's mental health topics. While our inclusion criteria vary slightly depending on the quality and quantity of research for any given topic, when we assess how well an intervention works, we rely on randomized controlled trials (RCTs). We do so because RCTs allow us (and others) to be sure that if children experienced improvements, it was due to the intervention rather than other factors such as chance. In this particular issue, we also outline an added criterion for classifying medications as being "supported by the research evidence." Namely, we required two or more published double-blind RCTs, including one with placebo controls, showing positive results in children or youth. We added this criterion because double-blind, placebo-controlled RCTs allow us (and others) to be sure that if children experienced improvements, it was due to medication rather than other factors, such as children's, parents' or researchers' expectations that the medication would work.

Table 2 summarizes our research findings. Specifically, four newer antipsychotics have been shown to be effective in treating five specific mental disorders in children and youth. Where other newer antipsychotics and other mental disorders are not listed, it means that we found insufficient high-quality research evidence supporting the medications' use.

Table 2: Newer Antipsychotics: Research Evidence on Effectiveness in Children and Youth

Medication	Disorders where medication is effective*
Aripiprazole**	• Autism spectrum disorder (associated challenging behaviours) in children and youth[22, 23] • Bipolar disorder (core symptoms) in youth[24, 25]
Olanzapine	• Schizophrenia (core symptoms) in youth[26–28]
Quetiapine	• Bipolar disorder (core symptoms) in youth[29, 30] • Conduct disorder (core symptoms) in youth[31, 32]
Risperidone	• Autism spectrum disorder (associated challenging behaviours) in children and youth[33–37] • Bipolar disorder (core symptoms) in youth[38, 39] • Conduct and oppositional defiant disorder (core symptoms) in children and youth[41–44] • Schizophrenia (core symptoms) in youth[27, 28, 40] • Tic disorder (core symptoms) in children and youth[45, 46]

* The medication has been studied in 2+ published double-blind randomized controlled trials, including 1 with placebo controls. Each trial showed positive outcomes related to these specific disorders or symptoms in children or youth.
** This medication has Health Canada approval for treating youth with either bipolar disorder or schizophrenia.

How does current prescribing compare with regulations and research?

Returning to the BC and Manitoba findings, to summarize, the top three antipsychotics being prescribed in each province (in the final study year) were risperidone, quetiapine and olanzapine (all newer antipsychotics). Meanwhile, the top mental disorders being treated with these medications (in the final study year) were depression, ADHD and anxiety in BC; and ADHD, conduct disorders (including ODD) and tic disorders in Manitoba. While other antipsychotics were also used and other disorders were also treated, these were by far the most common medications and uses. So how do these pediatric prescribing patterns compare with both the regulatory approvals and the research evidence?

Regarding regulatory approvals, Health Canada lists only aripiprazole — which was approved for treating youth with bipolar disorder or schizophrenia in 2009. Therefore, according to these BC and Manitoba studies, almost all newer antipsychotic prescribing for Canadian children and youth was off-label.

But a different picture emerges when we examine the best available research evidence on the newer antipsychotics. As outlined in Table 2, the research evidence suggests that four newer antipsychotics can be effective in pediatric populations: aripiprazole, olanzapine, quetiapine and risperidone. The research evidence also suggests very particular indications for these medications (i.e., bipolar disorder, schizophrenia, autism spectrum disorder, and conduct or tic

Four newer antipsychotics have been shown to be effective in treating five specific mental disorders in children and youth.

disorder). The research evidence therefore points — with considerable specificity — to which newer antipsychotics may indeed be appropriate for which disorders.

How do the BC and Manitoba findings overlap with this research evidence? Unfortunately, the studies' authors did not specify which medications were specifically prescribed for which disorders. So it is not possible to draw conclusions beyond looking at the top three medications and the top diagnoses.

When we examine the top three antipsychotics being prescribed, there is high-quality research evidence supporting the use of each of them, but only for specific purposes. It is therefore possible that these three medications may have constituted appropriate choices — if they were used for the specific purposes noted in Table 2. However, it is not clear why there would be three- to four-fold increases in these prescriptions for children and youth in recent years. These increases are quite remarkable given that there is no evidence from high-quality epidemiological studies of similar increases in the prevalence of pediatric mental disorders during this time.[17, 47, 48] These prescription increases are therefore highly concerning because they strongly suggest that research evidence was not the primary factor guiding off-label antipsychotic prescribing.

Newer antipsychotics should only be used where there is solid evidence that the benefits exceed the risks.

Identifying treatments backed by research evidence

Of even greater concern, newer antipsychotics are *not* recommended for treating three of the top five diagnoses identified in the BC and Manitoba studies (depression, ADHD and anxiety) in young people. Instead, for depression, CBT, interpersonal psychotherapy and adjunctive antidepressant medication (i.e., fluoxetine) are highly effective[49, 50] For ADHD, stimulant medications (methylphenidate, dextroamphetamine and atomoxetine) as well as behavioural therapy and parent training are highly effective.[51, 52] For anxiety, CBT is highly effective.[53] For young people with anxiety who do not respond to this treatment, adjunctive antidepressant medication (i.e., fluoxetine) may also be helpful.[54]

In contrast, there is research evidence supporting the use of some newer antipsychotics to treat the other top two diagnoses — conduct disorders (including oppositional defiant disorder) and tic disorders. Risperidone can effectively treat both conduct and tic disorders, while quetiapine can reduce symptoms of conduct disorder. [31, 32, 41–46]

Evidence supporting the use of psychosocial treatments for both conditions also exists. Multiple RCTs have shown the effectiveness of numerous psychosocial treatments for conduct disorder — including parent training, family therapy and CBT.[55, 56] Beyond the large number of high-quality studies supporting the use of these psychosocial treatments for conduct disorder, other advantages have been documented. Specifically, unlike antipsychotics, these psychosocial treatments

have been shown to lead to enduring benefits once the treatment ends. They also do not have the detrimental side effects common with antipsychotics.[19, 55, 56] Regarding tic disorders, evidence supporting the use of psychosocial treatments was more limited. However, we still uncovered two RCTs which showed that behavioural treatments can significantly reduce tics in children and youth.[57, 58]

First do no harm

Prescribing newer antipsychotics to children and youth may lead to harm in several possible ways. Most importantly, if using these medications means that effective treatments are inadvertently withheld — particularly for anxiety, ADHD and depression — then young people may experience needless suffering. Similar issues apply if newer antipsychotics are offered for conduct, autism spectrum and tic disorders without first offering other (first-line) effective treatments. For example, antipsychotics should be considered for children with autism spectrum disorder who experience severe behavioural symptoms only after appropriate behavioural treatments have been tried without success.[59]

Beyond inappropriate prescribing, there is also the question of basic safety. Newer antipsychotics, even in the short term, are associated with adverse health events for children and youth, including weight gain of 7 to 9 kilograms (15 to 20 pounds), abnormal blood glucose and lipid levels, and high blood pressure.[19] In fact, a recent prospective study of BC young people found that treatment with newer antipsychotics was a significant predictor for developing "metabolic syndrome" — a serious medical disorder associated with significant cardiovascular risks, including the development of type 2 diabetes.[60] Meanwhile, little is known about the longer-term effects of these medications, particularly when they are started early in life.[61]

Of course, no physician ever writes a prescription intending to cause harm. Still, given the side effect profiles of newer antipsychotics, the sharp rise in their prescriptions for children and youth has this potential — particularly if effective treatments are not being offered.[7] Newer antipsychotics should therefore only be used where there is solid evidence that the benefits exceed the risks. The BC and Manitoba studies suggest that beyond individuals, there may also be a public health problem in that for too many children and youth, this careful deliberation is not occurring.

Improving monitoring and prescribing

Given the significant metabolic side effects associated with newer antipsychotics, it is essential for practitioners to carefully monitor every child and youth taking these medications. Yet researchers at BC Children's Hospital found that even on inpatient units, only 32% of children were receiving such monitoring.[62]

These researchers consequently developed a "metabolic monitoring protocol" for children being prescribed newer antipsychotics.[60] Their Metabolic Assessment, Screening and Monitoring Tool identifies suggested intervals for measuring height, weight, waist circumference and blood pressure, as well as blood tests for assessing glucose, lipids, and liver and thyroid functioning.[63] The use of this protocol was highly successful, increasing monitoring on the inpatient unit to 89%.[64] Following this effective inpatient implementation, training was then provided to community-based child and youth mental health teams in Vancouver.[64]

The gains made in the community-based clinics extended beyond significant increased monitoring.[64] Perhaps even more importantly, newer antipsychotic prescriptions also decreased by 58% — including far fewer cases where these drugs were prescribed for disorders without regulatory approval or research evidence supporting their use.[64] For example, before the training, 44% of children on these antipsychotics had a diagnosis of attention-deficit/hyperactivity disorder. After the training, this percentage fell to 24%.[64]

Beyond BC, this screening tool has now been incorporated into Canadian pediatric and child psychiatry clinical guidelines for monitoring newer antipsychotics.[64] This screening tool therefore has considerable potential to improve monitoring and prescribing — particularly for family physicians in primary care.

Recommendations on using newer antipsychotics

Based on this review of the research evidence, only four newer antipsychotics should be prescribed for children and youth, and only for the following five specific conditions.

1. For youth with schizophrenia who exhibit core symptoms of psychosis (risperidone or olanzapine).
2. For youth with bipolar disorder who exhibit core symptoms of mania (risperidone, quetiapine or aripiprazole).
3. For youth with conduct disorders who exhibit core symptoms of severe aggressive behaviour — who have *not* responded to first-line treatments such as parent training, family therapy and CBT (risperidone or quetiapine).
4. For children and youth with autism spectrum disorder who exhibit challenging associated behaviours such as self-injury — who have *not* responded to first-line behavioural treatments (risperidone or aripiprazole).
5. For children and youth with tic disorders — who have *not* responded to first-line behavioural treatments (risperidone).

When prescribing any of these medications, the physician must also carefully monitor for side effects as well as benefits.

Beyond these specific uses, based on this review of the research evidence, newer antipsychotics are not recommended for children and youth. Instead, children and youth who experience anxiety, ADHD or depression should be offered effective first-line treatments for these conditions.

1. For children and youth with anxiety, CBT is the recommended first-line treatment, with fluoxetine being recommended for those who do not respond to CBT.
2. For children and youth with ADHD, stimulant medication is the recommended first-line treatment, with behavioural therapy and parent training also being effective.
3. For children and youth with depression, CBT is the recommended first-line treatment, with interpersonal therapy also being effective, and with one antidepressant (fluoxetine) being recommended for those who do not respond to psychosocial treatments.

For more information on effective treatments for anxiety, ADHD and depression, please see previous issues of the *Quarterly*.

For youth, parents and practitioners: What if you are concerned about a prescription?

Anyone — whether a youth, parent, teacher, health practitioner or social worker — concerned about a young person's prescription should speak directly with the prescribing physician. Most physicians ought to welcome this kind of inquiry and should be willing to provide a thoughtful rationale for their choices. Sharing this issue of the *Quarterly* may be helpful, too. In BC, you can also obtain additional good-quality health information from the following sources:

- HealthLinkBC website
- 8-1-1 — BC's free health information and advice line, which provides 24-hour access to nurses and other health professionals, such as pharmacists

When research findings and budgets collide

To the Editors:
In your recent issue on children in mental health crisis, the two interventions reviewed were delivered by practitioners with caseloads limited to three families. Yet child and youth mental health clinics typically do not have the staffing levels to support such resource-intensive interventions. How can these research findings inform our practice with children who are in mental health crisis?

Cheryl Conant
Surrey, BC

It can be quite challenging to implement new interventions at the best of times, but it is particularly difficult when resources are limited. One interim approach is to review the core elements of successful programs — to compare the new approach with current practices, and to determine what *can* be feasibly delivered. For example, the two successful interventions that we reviewed in the last *Quarterly* — *Home-Based Crisis Intervention* (*HBCI*) and *Multisystemic Therapy* (*MST*) — both contained elements that most child and youth mental health practitioners know well. These include cognitive-behavioural therapy, family therapy and parent training, as well as crisis intervention planning. Practitioners can focus on these strategies when they work with children in crisis — as many already do.

However, intensiveness is also a core element of these two interventions. For example, as you note, *HBCI* and *MST* both require strict limits on caseloads. This is likely an essential ingredient in the success of these programs, such that offering a less intensive version will not produce the same positive results. If this new approach cannot be feasibly delivered within existing resources, then a case needs to be made for more resources.

The bottom line is that research-informed practice requires adequate resources so that practitioners can indeed offer the best possible interventions for young people in need. For children in crisis, offering effective interventions such as *HBCI* and *MST* — with fidelity — may well save money in the long term, for example, by averting more costly hospital stays. But even more importantly, perhaps these interventions (and their intensiveness) need to be a model for expanding services and for organizing services differently — if children in crisis are not being well served.

Research-informed practice requires adequate resources so that practitioners can offer the best possible interventions for young people in need.

Contact Us

We hope you enjoy this issue.
We welcome your letters and suggestions for future topics. Please email them to chpc_quarterly@sfu.ca
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1. Identifying studies on psychiatric prescribing patterns

To identify psychiatric prescribing patterns pertaining to Canadian children and youth, we conducted a comprehensive search for systematic reviews and original population-based studies (i.e., covering all children and youth in a given region). In addition to our usual literature scanning, we searched major databases using the following search strategy:

Table 3: Search Strategy for Articles on Psychiatric Prescribing Patterns	
Sources	• Cochrane, CINAHL, ERIC, Medline and PsycINFO
Search Terms	• Off-label use and drug prescriptions
Limits	• Peer-reviewed articles published in English between 2003 and 2013 • Child participants aged 18 years or younger

Next we assessed all potentially relevant articles using the following inclusion criteria:

Table 4: Inclusion Criteria for Articles on Psychiatric Prescribing Patterns
Basic Criteria
• Relating to off-label prescription use or prescribing patterns in Canada • Describing both psychiatric medications and the diagnoses/conditions being treated

Using this approach, we identified three original studies — each assessing antipsychotic prescribing (one from BC and two from Manitoba). However, because there was considerable overlap between the two Manitoba studies, we extracted data from only the most recent one, which was also the most comprehensive.

2. Identifying newer antipsychotics with Health Canada approval

We first identified all the second-generation antipsychotics (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone) tracked in the two included studies on prescribing patterns. To determine which had regulatory approval for use in children and youth, we then searched the Health Canada Drug Product Database and reviewed all relevant product monographs pertaining to these seven medications.

3. Identifying research evidence on newer antipsychotics

We also conducted a comprehensive search to identify high-quality research evidence on the effectiveness of these seven second-generation antipsychotics for treating mental disorders in children and youth. Using methods adapted from the *Cochrane Collaboration*[65] and *Evidence-Based Mental Health*,[66] we applied the following search strategy:

Table 5: Search Strategy for Research Evidence on Newer Antipsychotics	
Sources	• Medline and PsycINFO
Search Terms	• Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone
Limits	• Peer-reviewed articles published in English between 2003 and 2013 • Child participants aged 18 years or younger • Randomized controlled trial (RCT) methods used

We then applied the following inclusion criteria — requiring medications to meet *all* criteria to be included in our final review.

Table 6: Inclusion Criteria for Research Evidence on Newer Antipsychotics
Criteria for RCTs
• Clear descriptions of participant characteristics, settings and medications • Use of double-blinding procedures • Attrition rates below 20% at post-test or use of intention-to-treat analysis • Outcome indicators relevant to specific mental health diagnoses • Levels of statistical significance reported for all primary outcome indicators
Criteria for defining medication effectiveness
• Two or more double-blind RCTs available showing significant positive benefits • At least one RCT available using placebo controls

Following the searches, two independent assessors reviewed all abstracts and all original retrieved articles — first reaching consensus on whether RCTs met the criteria, then reaching consensus on whether medications met the criteria. A final list of medications was then compiled.

For more information on our research methods, please contact

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BC government staff can access original articles from BC's Health and Human Services Library.

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