Optimizing care for patients in Canada with severe, persistent mental illness: a focus on pharmacologic therapy

Research Report and Summary from a National Multi-Stakeholder Roundtable

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IHE INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

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Executive Summary:

Severe, persistent, mental illness (SPMI) does not refer to a specific mental disorder, but is an umbrella term that describes mental illness associated with significant impairment in activities in daily living, and requiring treatment over a prolonged period of time, typically 2 or more years. SPMIs include schizophrenia, depression, bipolar and other debilitating mental disorders. Adults with SPMI have almost double the risk of dying from natural causes at any given age, compared with the general population.

Pharmacologic therapy is a mainstay of treatment for most patient with SPMI. Optimal treatment is influenced by many factors including: care navigation for patients, shortage of specialized treatment and outpatient care, the stigma of treatment, costs of treatment, intolerance to and lack of effectiveness from medication.

Good prescribing practices emphasize adherence and persistence to therapy as non-adherence is associated with hospitalization, risk of disease progression and death. To improve treatment persistence, prescribing physicians focus on reducing adverse events, ongoing monitoring, and individualization of medication to patients, including consideration of patient preferences.

The need to individualize care due to highly variable responses and side effect profiles in patients and has led to an even larger number of available pharmacologic therapies with different benefit/harm profiles.

While there appears to be clear recognition in Canada of unmet needs for individuals suffering from SPMIs and the need to provide high quality related services to address their needs, a number of issues related to optimizing care for patients with SPMI still exist. These include:

Key Points

- Severe and persistent mental illnesses are perceived to be more complex than many other health conditions because they impact multiple societal domains--- family, society, housing, mental health legislation, justice, individual rights
  - → **This complexity speaks to a more holistic approach to care that spans beyond Canadian healthcare systems**
- A number of issues represent challenges to optimizing the use of pharmacologic therapies including: how care is organized, how new therapies are evaluated, how patients and payers perceive the need for new therapies differently, the lack of access to therapies available in other markets, the costs of medications and policies that do not address equitable access.
- A number of actions that could lead to positive outcomes for patients were identified and would require leadership from all stakeholders including Federal and Provincial governments (including Health Canada), public and private payers, health technology assessment (HTA) bodies and manufacturers and care coordination programs.
  - → **These actions highlight the need for interventions that extend beyond healthcare systems, recognize the need for equitable and accelerated access as well as individualized care and choice, the need for better deliberative processes, and the need for less financial burden for patients**

- **Organization of care –** Patients with SPMIs have barriers to optimal care associated with social determinants of health including lower education and housing levels.
- **Understanding value -** The unique impact of individualizing therapy may not be well captured by clinical trials and the HTA bodies that assess these to support reimbursement and pricing decisions.
- **Separating patient need from patient demand**–many patients and care providers feel they might benefit from treatments that have not been reimbursed by public payers. This could reflect patients and providers not having access to confidential or proprietary manufacturer information, or that the population-based approaches used by HTA bodies do not adequately recognize the potential value of individualizing treatments.
- **Lack of availability of therapies –** some therapies are not available in Canada which requires greater examination to determine why manufacturers may have opted not to market them in Canada or characteristics of reimbursement processes that might reduce availability.
- **Reducing costs–** Costs of medicine to patients are a significant factor in non-adherence, which is already a significant factor in optimizing therapy for patients with SPMIs.
- **Enhancing equity –** There may be policies that do not recognize the need to provide equitable treatment to marginalized populations that typically have SPMIs.

To identify what supports are needed the most, the IHE conducted a facilitated, evidence-informed discussion that focused on the issue of optimizing care for those dealing with severe persistent mental illness (SPMI), with a focus on pharmacological therapies. The discussion included 13 invited representatives of multiple stakeholders including patient representatives (n=4), care providers (n=2), policy researchers (n=1), HTA bodies (n=1), health care administrators/policymakers (n=3), and manufacturers (n=2). A background paper was circulated to individuals prior to the meeting and a virtual meeting was hosted by the Institute of Health Economics on April 25th, 2024.

The Roundtable discussion followed the Chatham House rule to support frank discussion among invited participants. It was not intended to be a consensus exercise, but instead capture some key ideas and opinions from knowledgeable informants to inform ongoing work in this area.

The discussion focused on two questions:

1. **What key policy areas** outside of medication access merit ongoing engagement and collective strategy development to support this population?

2. **What key actions do you recommend** to accelerate access for Canadian patients to new cost-effective therapies in this area? (including assessment bodies, public payors, prescribers, patients and manufacturers).

Key findings from the discussion

Policy areas

- Severe and persistent mental illnesses were seen as more complex than many other health conditions because they impact multiple societal domains--- family, society, housing, mental health legislation, justice, individual rights.

- This complexity implies a need for more comprehensive, evidence-based interventions and a population health approach (endorsed by Canadian public health bodies) that would require changes at all levels of government, and that emphasizes determinants of health, intersectoral collaboration (including care coordination and integrated care), large-scale educational strategies, and accountability for outcomes.

- Certain mental health protocols are moving away from diagnostic based treatment to symptom-based treatment which means reimbursement criteria for existing drug therapies may require revisiting.

Key actions

The discussion highlighted potential actions from all stakeholders involved. These include:

Issue identified	Potential Action	Who should take action?
Choice and unencumbered access to effective treatments may be important attributes of new therapy that require consideration.	Consider evidence that demonstrates the impact of choice and access on population health outcomes.	Health Canada HTA bodies Provincial payers
Not all drugs are being brought by manufacturers to the Canadian market.	Investigate further reasons that companies decide not to bring drugs to Canada to help understand what may need to be changed.	Health Canada Manufacturers Public and private payers
Even when drugs are available, patients may not be able to access them equitably due to different insurance program requirements.	Federal Pharmacare program should consider offering first dollar coverage for patients with SPMI.	Federal government Public and private payers
A population health approach to SPMIs requires an outcomes accountability framework.	A registry could be considered to assess the quality of any future initiatives and impact to patients.	Federal government Provincial governments
Community-based coordination is an important and utilized service but does not have a sustainable finance model	Provincial governments should consider how to support these (largely charities) as part of an integrated care approach	Provincial governments Care-coordination programs
Some aspects of care require coordination across provincial government Ministries responsible for health care, justice, and social supports.	Provincial governments should consider creating unique Ministries or encouraging Inter-Ministerial arrangements that address the need for coordination for SPMIs.	Provincial governments

The value of psychotherapy along with the value of relational approaches to care and delivery are under-recognized.	Incenting multidisciplinary response teams, social supports tied to care, and through reorganization and novel financing models.	Provincial governments
Unique approaches to care for SMPI patients may also require unique approaches for drug reimbursement and access.	Special funding models may need to be considered for these medications.	Provincial governments
There is a need for accelerated access to new medicines, given the need for options, highly variable responses to medications and the "trial and error" approach to prescribing.	Special evaluation models such as Canada's Drug Agency (CDA-AMC)'s "Target Zero" (parallel review with regulator), and time limited recommendations should be recognized and utilized for new drugs for SMPIs.	Health Canada Public and private payers HTA bodies
Patient, family, and other circumstances tied to the need for new medicines may be underrecognized. SPMI patients and families are often marginalized and patient advocates may have fewer resources.	Improving deliberative processes including a broader range of stakeholders (e.g., more clinicians and families) along with better inputs (e.g., through advisory bodies or listening exercises).	HTA bodies
The value of choice and variability of response to medication may be overlooked by HTA bodies using population health/average approaches to assessing outcomes.	HTA bodies could supplement traditional approaches to examining trials with approaches to ascertaining individual value. Manufacturers could go beyond the minimal design in trials posed by regulators to better address variability. Payers and manufacturers and could consider innovative risk-sharing approaches.	HTA bodies Drug manufacturers Public and private payers
The prices of new therapies can impact persistence on medication, even with patient co-pays.	Drug companies need to reconsider their pricing model for drugs for SPMI. First dollar coverage models should be considered by private and public insurers, or through product listing agreements.	Drug manufacturers Public and private payers

1. Context

What are severe, persistent, mental illnesses?

Severe, persistent, mental illness (SPMI) does not refer to a specific mental disorder, but is an umbrella term developed in the mid-1980s by the US National Institute for Mental Health to describe mental illness that leads to significant impairment in activities in daily living, and treatment over a prolonged period of time, typically 2 or more years.[1–3] Diagnoses among people with SPMI include schizophrenia, depression, bipolar disorder, some personality disorders, post-traumatic stress disorder, and anorexia nervosa.[4]

Morbidity, hospitalization and loss of life

Adults with SPMI have almost double the risk of dying from natural causes at any given age, compared with the general population.[5–7] They are also at higher risk of death from unexplained injury, suicide, and homicide as well as cancer, circulatory, respiratory, and infectious disease.[5] Individuals with SPMI also have a higher rate of social problems, including alcohol and substance abuse, homelessness, lack of family support, and incarceration which all contribute to making equitable access to treatment more challenging.

Box 1 Example – a patient's journey with severe, persistent mental illness[8–10]

John is a 34-year-old man raised by a single mother outside of Toronto who was a promising track and field athlete. At 22, he began a history of drug and alcohol abuse and dropped out of college. At the same time, he began to show signs of mental illness and was diagnosed with schizophrenia. His symptoms, all rated severe, included auditory and visual hallucinations, delusions of persecution, apathy, social withdrawal, and reduced speech). He cycled through a number of antipsychotic drug treatment regimens, which is common practice given variable responses across individuals. All with some degree of effect, but never with complete symptom relief.

Over the next 12 years, John became paranoid and estranged from friends and his mother, had multiple encounters with law enforcement, and was unable to continue to live the independent life he wanted. Frustrated, fearful, isolated, and unstable, he made an attempt at his own life by stabbing himself. John was rushed to the emergency room. His injuries to the stomach, pancreas, and other organs were surgically repaired, and he was admitted to intensive care, sedated and on a ventilator. Psychiatry was asked to see him as soon as he was stabilized. During the initial interpreter-assisted interview, he exhibited fear, anxiety, and paranoia, prompting placement of an involuntary psychiatric hold.

Throughout his hospitalization, he maintained that he was being treated against his will and pleaded with his mother at bedside to advocate for his wishes. Often, his agitation would escalate to the point of requiring physical restraints, an intervention that, in this case, brought its own added dimension of suffering. After his initial surgical stabilization and related medication use, he was found to have a postoperative biliary leak which led to sepsis. Doctors, concerned for his life, consulted with a palliative care team. In consultation with the ethics committee, his mother settled on a de-escalation strategy: withdrawal of mechanical life support with time-limited continuance of intravenous antibiotics and fluids. Within two days, his respiratory function began to falter from acute respiratory distress syndrome, and he remained persistently febrile. The patient was transferred to an in-patient hospice facility where he died a few days later.

Standards of care

While there are no specific Canadian consensus clinical guidelines for SPMI, there are a number of individual guidelines for the disorders that underly SPMI are diagnosed with.[11–17] For patients with schizophrenia, this guidance emphasizes intensive, and timely care with access to a comprehensive range of services that include "psychological, pharmacological, social, occupational and culturally safe interventions [11].

Pharmacologic therapy is a mainstay of treatment for most and emphasizes adherence and persistence to therapy as non-adherence is associated with hospitalization, risk of disease progression and death. To improve compliance with medication, prescribing physicians focus on reducing adverse events, ongoing monitoring, and individualization of medication to patients, including consideration of patient preferences.[18]

Provincial priorities and Canada's Mental Health Strategy

In 2006, the Senate standing committee on social affairs, science and technology completed the country's first study of mental health, mental illness, and addiction: Out of the Shadows at Last: Transforming Mental Health, Mental Illness and Addiction Services in Canada.[19] The report described the burden and stigma of mental illness, its legal and research implications, access to care and the need for strategic planning and intergovernmental coordination. This led to the development of the Mental Health Commission of Canada and its 2012 pan-Canadian strategy for mental health.[20] The strategy outlines six strategic directions for Canada including addressing needs for remote and indigenous communities, and providing access to the right combination of services, treatments and supports, when and where people need them.

In May 2012, the Sixty-fifth World Health Assembly adopted resolution WHA65.4 on the global burden of mental disorder leading to a call from the WHO for a comprehensive, coordinated response from health and social sectors at the country level in 2013. After 2015, and the Federal election of the Liberal government, Canadian Health Transfer agreements have continued to emphasize mental health as a shared F/P/T priority with dedicated funds to improving access to mental health and addictions services since 2017. This includes Budget 2021 providing nearly $1B towards mental health care funding and specific commitment of $4.5B over five years for first-ever Canada Mental Health Transfer.

This has led to improving provincial infrastructure, such as Ontario's investment in youth and children and it structured psychotherapy network.[21] Despite this increasing emphasis on improving mental health services, the availability of services and qualified professionals, particularly for marginalized populations, continues to be a significant policy challenge.[22]

In Alberta there has been a significant focus on Mental Health and Addictions with the creation of separate Ministry and Cabinet portfolio and new organizational infrastructure targeted to address those dealing with mental health and addictions.
https://www.alberta.ca/release.cfm?xID=900733836BB31-FF75-960D-1AF0446E29A789FE

The significant work done through the Mental Health Addictions and Advisory Council in Alberta emphasize the need to increase coordination for supports for those living with mental illness. These bodies have suggested that "*Like chronic illnesses such as diabetes or coronary artery disease, addiction and mental illness such as schizophrenia or opioid use disorder typically require long-term management*".

They have also stated: "*The overarching goal is to convert our current disparate supports and services into a coordinated network providing a continuum of supports (prevention, early intervention, harm reduction, treatment and recovery) for people at risk of or suffering from addiction and mental health challenges.*"

Role of pharmacologic therapy

Unmet Needs

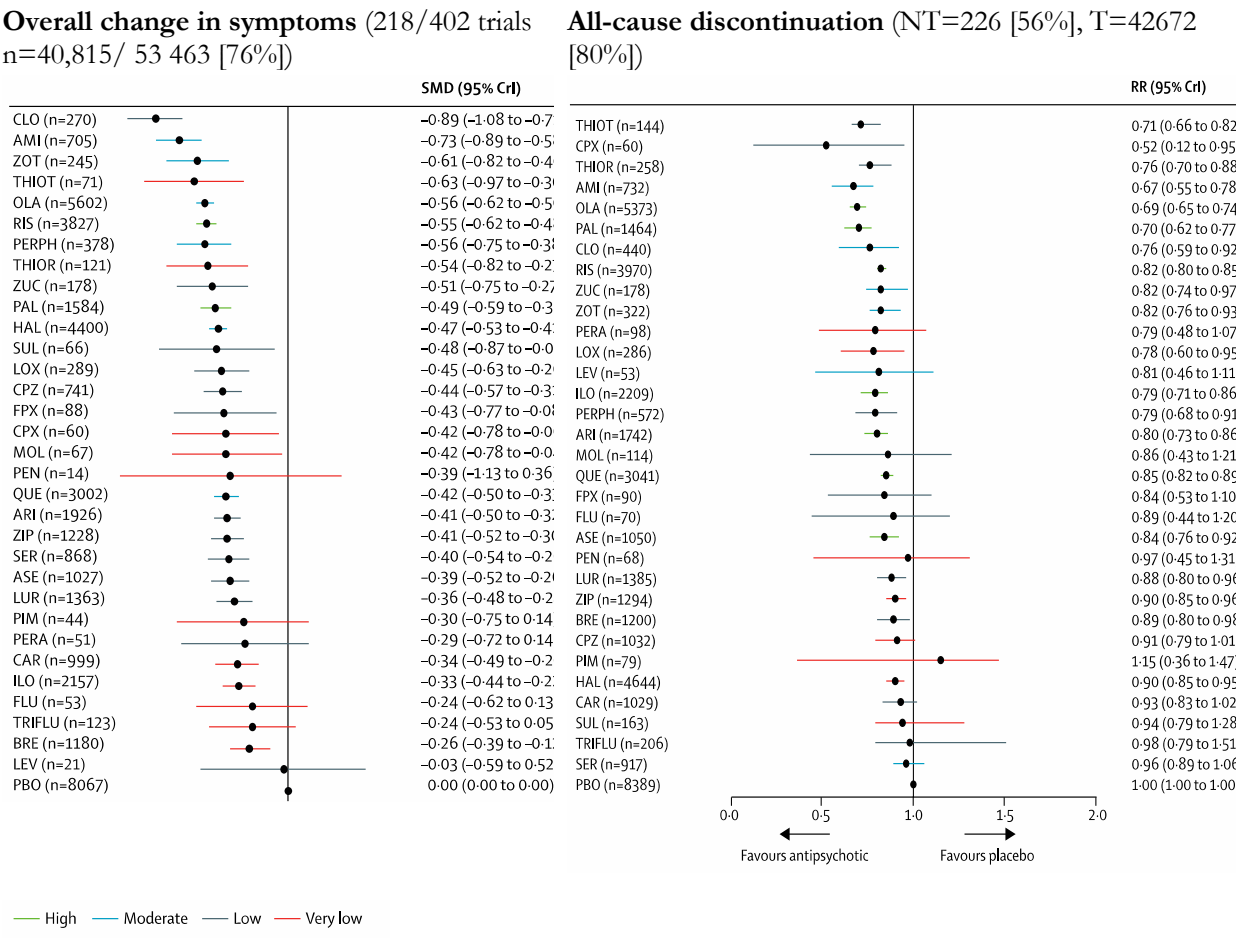
The treatment of mental illness and addictions is complex and is influenced by many factors including: care navigation for patients, shortage of specialized treatment and outpatient care, the stigma of treatment, costs of treatment, intolerance to and lack of effectiveness from medication.[23,24] Most people suffering from mental illness require some support from pharmacologic therapy and ongoing compliance is an issue where appropriate supports are needed for ongoing management.

Pharmacologic treatments for chronic and severe psychoses and mood disorders appear on the WHO Model List of Essential Medicines. The need to individualize care due to highly variable responses and side effect profiles in patients and has led to an even larger number of available pharmacologic therapies with different benefit/harm profiles.

Effectiveness of Current Treatment Options

The largest and most widely cited analysis of pharmacologic treatments for treating symptoms in the acute phase of schizophrenia (for example) is based on 402 studies including 53,463 participants randomly assigned to 32 different older and newer antipsychotics or placebo.[26] The analysis reveals some differences in the average effectiveness of treating symptoms with more marked differences in side-effects and discontinuations. It also reveals a wide variation in the confidence of evidence, when key factors such as bias, imprecision, heterogeneity and incoherence were considered. Despite some encouraging effects, up to 70% of patients may not persist with therapy within a year of treatment initiation, due to a variety of patient, social and clinical factors.[25] An analyses of maintenance treatments of the same 32 medications reveals a similar pattern of variation.[43]

Figure 1 Relative effectiveness of current pharmacologic treatment options for schizophrenia, based on randomized controlled trials[26]



Colours indicate the confidence in the evidence: green=high, blue=moderate, grey=low, red=very low.

Treatments are ranked according to their surface under the curve cumulative ranking and compared with placebo. Effect sizes are presented as standardised mean difference or risk ratio with 95% CrIs. The evidence is graded using the CINeMA system (Confidence in Network Meta-Analysis), an adaption of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach for network meta-analysis. NT=total number of trials reporting the outcome (percentage of sample). nT=total number of participants available for the respective outcome (percentage of sample). SMD=standardised mean difference. CrI=credible interval. RR=risk ratio. AMI=amisulpride. ARI=aripiprazole. ASE=asenapine. BRE=brexpiprazole. CAR=cariprazine. CLO=clozapine. CPX=clopenthixol. CPZ=chlorpromazine. FLU=fluphenazine. FPX=flupentixol. HAL=haloperidol. ILO=iloperidone. LEV=levomepromazine. LOX=loxapine. LUR=lurasidone. MOL=molindone. OLA=olanzapine. PAL=paliperidone. PBO=placebo. PEN=penfluridol. PERA=perazine. PERPH=perphenazine. PIM=pimozide. QUE=quetiapine. RIS=risperidone. SER=sertindole. SUL=sulpiride. THIOR=thioridazine. THIOT=thiothixene. TRIFLU=trifluoperazine. ZIP=ziprasidone. ZOT=zotepine. ZUC=zuclopenthixol.

Economic impact of new treatments

Numerous economic evaluations have been developed to help policymakers understand the costs and consequences of the use of therapy. Additional costs in these evaluations typically include the costs of medicine, the cost of treating adverse events including movement disorders, weight gain, and metabolic side effects. Avoided costs in these evaluations are due to reduced use of psychiatric service, sheltered accommodation, suicide attempts and work productivity.[27,28]

While these analyses suggest most antipsychotics have the potential to be cost-effective, the vast majority of analyses have been shown to have "very serious" quality limitations due to not including all relevant costs, or outcomes, or not adequately modeling disease such as discontinuation due to intolerability or non-adherence.[27] Some of these challenges are a reflection of challenges with underlying data (i.e., lack of long-term or generalizable clinical or resource impact [27,28] data). Also, many standard-of-care medications are now generic so newer therapies need to be reasonable in valuation approaches in the enhanced benefit they provide compared to what are now lower cost alternatives in pricing.

Factors associated with optimizing pharmacologic care for patients

Demand-side factors

There are several well-documented factors that may influence patient demand for pharmacologic care.[29] A key factor is awareness and acceptability of SPMI diagnoses by individuals with disease and within society itself.[30] These barriers lead to reduce help-seeking behavior and are bolstered by low education and low income, which are more prevalent in an SPMI population.[31] It may also lead to poor recognition of the effectiveness of treatment for mental disorders.

Reduced help-seeking is also a consequence of stigma and discrimination from having a diagnosis associated with SPMI.[29,32] This factor is exacerbated by the high symptom burden of suffering with a disorder associated with SPMI as , for example, symptoms of major depressive disorder are linked to having no energy or motivation to seek help. Some individuals additionally experience social anxiety and agoraphobia, exacerbating the problem.[29] Others may have substance abuse issues including a history of alcohol dependency that is associated with non-adherence to medication.

For individuals who have sought help and are successfully taking therapy, SPMI can still lead to poor treatment adherence due to a variety of factors including a lack of social supports, side-effects, limited insight, and diminished cognitive functioning.[33] Complexity and length of treatment are also key factors. Patients with SPMI may also have significant physical co-morbidities, limiting mobility and creating challenges with adherence.[29]

A final factor are the costs associated with therapy. Of Canadian patients who have filled 1 prescription, 8.2% report being able to afford 1 or more drugs.[34] Drugs for mental health conditions were the most commonly reported drug class for cost-related nonadherence. Cost-related non-adherence is a particular challenge for younger people, those with severe disease and those without drug insurance and is not limited to newer, more expensive medications.[34]

Supply-side factors

The ability of the healthcare system[24] to supply medicines to patients with SPMI is also influenced by a number of factors. Healthcare systems may lack adequate systems of navigation, or have long wait times for an ever-increasing scarcity of health professionals. There may also be a lack of service organization and cultural and language barriers.

The significant cost impact to health systems of new medicines in Canada has led to the use and adoption of health technology assessment (HTA) organizations to facilitate the rational selection of medicines, consistent with WHO guidance.[33,35] In Canada, HTA bodies significantly influence public payer decisions, particularly for new medicines for SPMI. An examination of HTA recommendations between 2012-2022 reveals a large proportion (54%, 7/13) of negative recommendations for new drugs to treat disorders associated with SPMI and that this is a higher rate of negative recommendation than recommendations for drugs for non-mental health indications. (17%, 67/384).[36]

While some have expressed concerns this represents a significant gap in access to care[36,37], HTA bodies have been clear on the reasons for these negative recommendations which largely relate to limitations in evidence consistent with concerns about rational and efficient drug use (Table 1).

Table 1 CDA-AMC reasons for negative recommendations of new drugs for patients with SPMI (2012-2022)

Generic (Brand) Name	Therapeutic Area	Date	Unmet needs identified	Reason(s) for Negative Recommendation
Asenapine (Saphris)	Schizophrenia	14-Jun-2012	• Need for increased productivity • Reduced sleepiness and weight gain	• "failed to consistently demonstrate superiority ..in five placebo-controlled trials" • Olanzepine was superior in one of three trials.
Lurasidone* (Latuda)	Schizophrenia	23-Jan-2013	• Need for better activities of daily living • Emotional burden for caregivers • Reduced side effects	"…insufficient evidence from randomized controlled trials (RCTs) to establish the comparative efficacy of lurasidone relative to other less costly antipsychotics"
Zolpidem (Sublinox)	Insomnia**	25-Sep-2013	• More effective or less toxic medicines • Reduced potential for dependence and next-day drowsiness	"…insufficient evidence to determine if sublingual zolpidem provides comparable clinical benefit versus other hypnotics available in Canada..."
Aripiprazole* (Abilify)	MDD	22-Oct-2014	• Fewer or no-worse side moderate to severe effects • Reduced potential for weight gain	• "…the magnitude of [symptom] improvement [vs. placebo] was limited and failed to … consistently [across 3 trials] exceed the minimal clinically-important differences …" • "The safety and efficacy of aripiprazole as an adjunctive treatment in MDD have not been evaluated in RCTs longer than six weeks" • There are no head-to-head trials.
Esketamine (Spravato)	MDD	16-Dec-2020	"There is a clear unmet need for effective and safe treatments for patients who have not responded adequately to sequential optimized antidepressant trials"	• "…[3 trials] did not demonstrate a consistent statistically significant benefit with esketamine in combination with a newly initiated oral antidepressant compared with placebo in combination with a newly initiated oral antidepressant" • "[trials] not designed… to evaluate several important patient-valued outcomes such as improvements in patients' health-related quality of life, improvements in daily activities or functioning, reduced suicidality, and hospitalizations or emergency department visits" • "… trials did not reflect those in whom esketamine would most likely be used in Canadian clinical practice…" • Greater proportion of patients experienced adverse events.
Cariprazine (Vraylar)	Schizophrenia	10-Aug-2022	"Patients expressed a need for treatments which minimize … symptoms of schizophrenia, provide an additional option for those who do not respond to existing treatments, are administered less often, and have fewer side effects."	• "it is not clear whether [observed symptom control and reduced relapse] result in a clinically meaningful improvement in patient-identified needs" • "There was not enough robust evidence to show that Vraylar filled a treatment gap" • "there were no clinical trials in patients with acute schizophrenia that compared Vraylar with any other treatments"
Cariprazine (Vraylar)	Bipolar disorder	9-Nov-2022	"Patients expressed a need for treatments that control the symptoms of bipolar I disorder, provide an additional therapy for those who do not respond adequately to existing drugs, lower the frequency of administration, and minimize side effects.	"it is unclear if patients treated with Vraylar in clinical practice would experience the same magnitude of improvement, as patients in the cariprazine studies may not represent the population of patients who will use cariprazine in Canada" "the results for the 3 mg dose of Vraylar were inconsistent across studies;" "There were no studies directly comparing Vraylar with any other treatments"

*subsequently positively recommended; **while not a mood disorder, per se, insomnia is heavily associated with SPMI

This does not apply to all products identified. More recent negative recommendations have highlighted the need for compelling evidence of benefit (including reduced harm from therapy) in patients unresponsive to existing care or versus other less-expensive treatments. There have also been concerns raised about treatments not being consistently effective or inferior to existing treatments.

Some concerns about the time taken to review have also been raised, although Canada's HTA process are the second fastest in the world and has become even faster more recently as manufacturers are now allowed to apply for formulary listing while under regulatory approval.[38] Despite this, an average time-to-patient access was observed to be 1,177 days, or just over three years for three selected medications (Trintellix, Invega Trinza, Abilify Maintena) reimbursed in all four of Canada's most populous provinces; however this timeframe is largely dependent on manufacturer decisions regarding the timing of a submission to payers and the price negotiation process, which has no regulated time limit.

An additional supply-side factor is related to the regulation and approval of medicines for sale. As with HTA, Canada exhibits relatively short times to approve new medicines compared to similar countries (Australia, England, France, Germany Sweden – 2014 -18).[38] However it is slower compared to the US—in Canada, a much smaller proportion of drugs that go through an expedited review process[39] and Canada reports average review times that are 100 days longer when multinational pharmaceutical company decisions to bring medicines to Canada.[40]

Given the large number of competitors and reluctance for public insurers to fund new medicines when comparative or generalizable evidence is lacking, manufacturers may decide not to pursue licensed indications in Canada. This has led to a situation where a number of new medicines and formulations for severe mental illness may be available in the rest of the world but not in Canada. It is not known whether public insurers would consider these valuable and want to adopt them.

Box 2 Some medications for patients with SPMI not marketed in Canada

- Iloperidone (Fanapt)
- Lumateperone (Caplyta)
- Olanzapine/Samidorphan (Lybalvi)
- Dextromethorphan/Bupropion (Auvelity)
- Olanzapine/Fluoxetine (Symbyax)
- Reboxetine (available through SAP)
- Brexanolone (Zulresso)
- Mianserin (Tolvon)
- Isocarboxazid (Marplan)
- Agomelatine (Ardix)
- Quazepam (Doral)
- Ramelteon (Rozerem)
- Suvorexant (Belsomra)
- Tasimelteon (Hetlioz)
- Zaleplon (Sonata or Zerene)
- Flunitrazepam (Rohypnol)

2. Issues with optimizing care

While there appears to be clear recognition in Canada of unmet needs for individuals suffering from SPMIs and the need to provide high quality services related to address their needs, a number of issues related to optimizing care may warrant further discussion:

- **Organization of care** – While Canada continues to create capacity to address SPMIs and other mental disorders, there is a need to recognize the social determinants and other demand-side barriers that relate to suboptimal care of patients with SPMIs, including lower education and housing levels, and how these factors relate to suboptimal care. Improving care navigation[24], providing social supports[41], and promoting the use of multidisciplinary community health teams through virtual care and assertive community treatment through hub and spoke models are proven strategies to optimize care for patients.[42] These strategies recognize that barriers to suboptimal care stem from demand for services which in turn stem from challenges that patients face when they have an SPMI.

- **Assessment of medications.** HTA processes do have a strong focus on a health system perspective in analyses – and there are some claims there is a lack of recognition of the unique clinical considerations for patients with SPMI and when conducting clinical trials in mental illness and a lack of recognition on the impacts on patient quality of life and broader societal cost avoidance factors. Outcomes are sometimes challenging to measure and can create uncertainty from assessors in the additional value provided for some interventions. There are some areas where treatment advancement has not occurred for some time and comparison is against low-cost generics. There are some claims of an undervaluing of the value provide by new medications in reduction in significant side-effect profiles.

- **Patient need versus patient demand and HTA** – Any public policy decision in healthcare must distinguish between patient *need*, which are dependent on the ability of a patient to benefit from healthcare, and patient *demand* which reflects preferences for healthcare services (and benefits) backed by an ability to pay. In Canada, HTA bodies have taken on the role of understanding how patients might benefit from new pharmacologic agents to inform those who might pay. As there are still patients who feel they might benefit from treatments that Canada's Drug Agency (CDA-AMC, formerly CADTH) has negatively recommended, this creates two possibilities:

    - The first is related to challenges with information asymmetry- it is possible that CDA-AMC through its access to confidential and technical information is more aware of potential benefits to patients than patients themselves are, and that they need to better engage patients in the HTA process to enhance understanding and legitimacy of recommendations. Transparency is important and CDA-AMC is working to enhance this its current processes related to deliberation and recommendation.

  - The second is that CDA-AMC's evidence-based approach to recommendations, which considers population-based metrics of benefits (i.e., average effects) is incompatible with some individualized approaches through how clinicians look at therapeutic applications. Heterogeneous responses in patient populations mean significant trial and error and choices to fit patient circumstances may improve overall outcomes. That is, even if a therapy is proven to be similar to existing therapies on average, it may still beneficial to an individual. It is possible that CDA-AMC needs to revisit frameworks that assess benefits in these patients to consider the value of individualized approaches to care.[43]

- **Better understanding of manufacturer decisions –** some supply-side issues of access relate to manufacturer decisions to apply to regulator s or HTA bodies. As private, for-profit organizations in a competitive environment, these decisions are not typically publicized. Research to better understand manufacturers' ability and willingness to supply to Canada could inform understanding of how to optimize medicines.

- **Reducing costs–** Costs of medicine to patients are a significant factor in non-adherence, which is already a significant factor in patients with SPMIs for reasons mentioned. Exploring progressive policies (e.g., first-dollar coverage through listing agreements, Federal pharmacare coverage) that will alleviate expenditures to patients may lead to better usage of pharmacologic therapy for patients with SPMI.

- **Enhancing equity –** As SPMI is already endemic to marginalized populations, policies that enhance equitable treatment beyond cost-reduction and re-organization of care warrant exploration.

3. Potential actions – Questions for discussion

To identify what supports are needed the most, the IHE conducted a facilitated, evidence-informed discussion that focused on the issue of optimizing care for those dealing with severe persistent mental illness (SPMI), with a focus on pharmacological therapies. The discussion included 13 invited representatives of multiple stakeholders including patient representatives (n=4), care providers (n=2), policy researchers (n=1), HTA bodies (n=1), health care administrators/policymakers (n=3), and manufacturers (n=2). A background paper was circulated to individuals prior to the meeting and a virtual meeting was hosted by the Institute of Health Economics on April 25th, 2024.

The Roundtable discussion followed the Chatham House rule to support frank discussion amongst invited participants. It was not intended to be a consensus exercise, but instead capture some key ideas and opinions from knowledgeable informants to inform ongoing work in this area.

The discussion focused on two questions:

1. **What key policy areas** outside of medication access merit ongoing engagement and collective strategy development to support this population?

2. **What key actions do you recommend** to accelerate access for Canadian patients to new cost-effective therapies in this area? (including assessment bodies, public payors, prescribers, patients and manufacturers).

The remainder of this report is organized as follows:

- **Section 4** Provides a summary of the key policy areas outside of medication access that merit ongoing engagement and strategy (Question 1, above)
- **Section 5** Describes the issues identified by theme actions to address these, and who may lead these actions. (Question 2, above)
- **Appendix A** provides a description of the Roundtable Agenda and attendees.

4. Policy areas outside of medication access that require focus

Participants described patients with severe and persistent mental illness as having more complex circumstances than many other health conditions. This is because their illnesses impact multiple societal domains. These include:

- Education, work, social life and interactions with their family - Families help to support the well-being of members who have SPMIs.[44–46] Emotional support is often provided by family members who themselves may experience stress or burnout.[47] People who care for family members with SPMIs report difficulties in providing care along with a negative impact on physical health, financial burden, rates of employment and quality of life when a family member has an SPMI.[48]

- The need for housing – People with SPMIs are disproportionately affected by homelessness. Interventions that assist with housing, such as supported housing facilities are associated with better mental and physical outcomes for patients.[49]

- Employment and the need for specialized legislation or programs to protect and support patients with mental health issues such as labour placement programs.[50]

- Legal issues – people with SPMIs have higher rates of criminal behavior, contacts with the justice system, and are more likely to be victims of violence-- particularly homeless adults with severe mental illness.[51]

In other words, the well-being of patients is not simply a product of a well-functioning health system, but creates strain on traditional social supports while creating the need for additional supports outside of the healthcare system.

Participants felt this complexity meant a more comprehensive, evidence-based interventions and a population health approach (endorsed by Canadian public health bodies) is needed and would likely require changes at all levels of government. These changes would need to emphasize the role of determinants of health, intersectoral collaboration (including care coordination and integrated care), large-scale educational strategies, and accountability for outcomes.

Some Roundtable participants also flagged changing paradigms of care; wherein mental health treatment protocols are moving away from diagnostic-based treatment to symptom-based treatment. This could affect current approaches to patient access through pricing and reimbursement criteria for existing drug therapies and may require revisiting current policies.

5. Issues and key actions for Canadian stakeholders

The discussion highlighted key issues and potential feasible actions to resolve from all stakeholders involved.

Federal government

The Federal government, through its role as a regulator of marketed medicines, has an important role in allowing access to new medicines for people with SPMIs. Participants noted that while it is ultimately up to drug manufacturers to apply to the Health Canada to market new therapies, it is clear not all manufacturers decide to do so. The reasons for this are not entirely known but may relate to either special restrictions posed by regulators or the potential for these medicines to be subsequently insured (by public and private drug insurance plans). Participants felt it would be helpful to investigate further reasons that companies decide not to bring drugs to Canada to help understand what may need to be changed to improve access.

If the evidentiary restrictions posed by Health Canada (or subsequently, public/private payers) are ultimately viewed as part of the challenge of bringing new medicines to Canada, some participants felt it might be worth revisiting these. In particular the question of whether the need and role of choice as an important attribute for pharmacologic therapy in this space may be overlooked, as some drugs that clinicians feel would be worth using (even if by trial-and-error) are still not marketed in Canada, but are available in other countries. An additional consideration might be the role of variability of response, as traditional population-based approaches to examining efficacy may overlook benefits to individuals.

Beyond Health Canada, the Federal government could also play a larger role through the implementation of its new Federal Pharmacare program. As the new Act introduced to support the first phase of Pharmacare proposed to provide universal, single-payer, first-dollar coverage for a range of contraception and diabetes medications[52], participants believed this mechanism should additionally consider expanding to SPMIs in subsequent phases. In doing so it would address issues of equity of access and lack of persistence with medication due to cost (i.e., co-pays) or in some cases, due to changing insurance programs (e.g., from private- to public insurance programs or from child to adult programs). The Federal government could additionally play an important role by supporting the development of registries or similar initiatives to track outcomes and care of patients. A true population health approach, such as that used in public health programs, highlights the need for accountability of outcomes, which may more difficult to understand in the current environment.

Provincial governments

Provincial governments can play a role in recognizing and taking actions to provide the various supports beyond the health care systems that they steward, required for patients with SPMI and highlighted in the previous section.

One key role for provincial governments is to re-examine support for interventions outside of the healthcare system that improve health outcomes. Participants suggested that provincial governments need to recognize the role of community-based coordination, which is largely run by charities, and how to sustain and bolster these. This was a clear theme in a statement by one participant: "But you have all of these community mental health organizations who provide peer support, … guidance, … counseling or therapies … [are] not considered part of the health care plans in or healthcare systems and these provinces and territories"

One solution highlighted was the need for more Inter-Ministerial cooperation across the various branches of government (e.g., health care, justice, and social service). Another solution proposed was the development of new Ministries or programs that can more easily integrate activities across departments. One participant stated "just because we have … independent ministerial portfolios in our system of government doesn't mean that we can't have integrated policy development and integrated budgeting".

Provincial governments and health care systems were also seen as having a key role in establishing multidisciplinary response teams, social supports tied to care, and reorganization and novel financing models of healthcare delivery in general that would be necessary to achieve intersectoral collaboration. In doing so, they may also create the basis of more integrated care that considers the role and value of psychotherapy and other non-drug measures (e.g., housing) that can bolster the effectiveness of medications. Participants noted that one shortcoming of current care approaches is that we use the same approach to funding interventions for mental illness as physical illness.

One such approach, highlighted by a Roundtable participant was a "relational approach" (i.e., emphasizing the importance of relationships between caregivers and patients) to care and delivery, given the need for trust by patients. One participant stated "the big system changes that need to happen in particular in this space, is [changing] our healthcare system to a relational model of care. We need to healthcare ... providers to [be] funded to give the time to these patients [and] have dedicated care assignments for these for patients with severe mental illness, so that they're allowed to develop a trust".

Health technology assessment (HTA) programs

Similar to issues raised regarding the Federal regulator's consideration of evidence, a key question arose related to clinical trials and trial design in mental health and whether they should be assessed using the same standards for other illnesses. That is, both Health Canada and key HTA bodies (e.g., CDA-AMC; Institut national d'excellence en santé et en services sociaux) use a population-based approach that considers average effects versus an individual patient-based approach that considers the ability of a drug to impact individuals given the need for trial-and-error and high variability of responses.[43] The flip side of this issue is one for manufacturers (described below), who may also need to consider providing more robust evidence to support these claims, beyond regulator-prescribed trial designs used today.

Another issue was the need for accelerated access to new medications. Some participants highlighted current programs, such as "Target Zero" that are attempting to do this through promotion and increased uptake of a parallel review of new drugs with regulators. While this is seen as one promising approach to get new medicines to patients faster, they still require companies to cooperate. This in turn can create challenges for companies who allocate internal resources toward regulatory and insurance activities sequentially, and may not have caught up to this new paradigm.

Other promising initiatives by HTA bodies include the CDA-AMC's new "time limited recommendation" program which seeks to provide conditional recommendations to provincial drug plan managers for new and promising medications that may have less robust evidence packages, but for which more evidence is expected. One participant commented that "we need … less rigid approaches to determining what those treatment options will be, what ones will be available".

Participants also highlighted the need for HTA bodies to recognize special patient, family, and other circumstances that may be tied to the need for new medicines. There was some concern that while patients and patient groups are currently involved in HTA processes, the larger social impact of SPMIs may necessitate exchange with families and other informal caregivers and supports. ("I think there needs to be some flexibility and consideration about how are we actually really going to reach into these marginalized communities to pull these types of insights into the HTA review") One proposed action was to work toward improving deliberative processes tied to HTA programs. In doing so, HTA bodies would have the opportunity to be more transparent about who has inputted into the process, how their opinions have been considered, and ultimately how judgments have been made.

Ultimately, it was felt that HTA bodies need to recognize that SPMI patients and families are often marginalized. In addition to patients who input into the process now, HTA bodies have an opportunity to consider the added perspective of families as they play an important role in these patients. Adding to the problem is that even current patient groups may have less resources available to support deliberation This was reflected in a comment by a participant: "there's a lot of mental health organizations who are not even involved in this because they can't afford to put their staff time into it". It was noted that the CDA-AMC has completed a listening exercise for mental health and is also currently improving deliberative processes that may address some of these issues.

Public insurance programs

While public insurance programs largely follow advice from their respective HTA organizations, they also have opportunities to enhance access through innovative risk-sharing approaches within their confidential product listing agreements with manufacturers that recognize highly variable responses across patients with SPMIs, as well as trial and error approaches and the need for choice. They can also insist on first-dollar coverage policies for current and future medications.

Drug manufacturers

As persistence with therapy is a key concern for care providers in achieving optimal outcomes for patients, there was a recognition that manufacturers need to consider how the price of any new therapy impact timelines for successful negotiations with public insurers as well as how costs to individuals (even through co-pays) impacts persistence with therapy. Drug manufacturers bringing new therapies into markets for patients with SPMI may need to revisit their pricing or negotiating formula used for non-SPMI drugs to avoid financial toxicity (i.e., non-persistence due to cost) by patients that leads to lower effectiveness.

Another issue for manufacturers is the evidence generation activities associated with new drugs. While much was said about the need for regulators and HTA bodies to revisit how they review evidence due to highly variable responses, it was also suggested that compelling evidence still needs to be provided. Manufacturers may have incentives to conduct trials in accordance with the minimal standards set out by regulators in larger markets (i.e., the US Food and Drug Administration and European Medicines Agency), however nothing is preventing them from investing in registries, or consider investments in more pragmatic trials that might include information beyond regulatory requirements.

A summary of potential actions is described in Table 2, below.

Table 2 Summary of Issues and Potential Actions Identified by Roundtable participants

Issue identified	Potential Action	Who should take action?
Choice and unencumbered access to effective treatments may be important attributes of new therapy that require consideration.	Consider evidence that demonstrates the impact of choice and access on population health outcomes.	Health Canada HTA bodies Provincial payers
Not all drugs are being brought by manufacturers to the Canadian market.	Investigate further reasons that companies decide not to bring drugs to Canada to help understand what may need to be changed.	Health Canada Manufacturers Public and private payers
Even when drugs are available, patients may not be able to access them equitably due to different insurance program requirements.	Federal Pharmacare program should consider offering first dollar coverage for patients with SPMI.	Federal government Public and private payers
A population health approach to SPMIs requires an outcomes accountability framework.	A registry could be considered to assess the quality of any future initiatives and impact to patients.	Federal government Provincial governments
Community-based coordination is an important and utilized service but does not have a sustainable finance model.	Provincial governments should consider how to support these (largely charities) as part of an integrated care approach.	Provincial governments Care-coordination programs
Some aspects of care require coordination across provincial government Ministries responsible for health care, justice, and social supports.	Provincial governments should consider creating unique Ministries or encouraging Inter-Ministerial arrangements that address the need for coordination for SPMIs.	Provincial governments
The value of psychotherapy along with the value of relational approaches to care and delivery are under-recognized.	Incenting multidisciplinary response teams, social supports tied to care, and through reorganization and novel financing models of healthcare delivery.	Provincial governments
Unique approaches to care for SMPI patients may also require unique approaches for drug reimbursement and access.	Special funding models may need to be considered for these medications.	Provincial governments
There is a need for accelerated access to new medicines, given the need for options, highly variable responses to medications and the "trial and error" approach to prescribing.	Special evaluation models such as Canada's Drug Agency (CDA)'s "Target Zero" (parallel review with regulator), and time limited recommendations should be recognized and utilized for new drugs for SPMIs.	Health Canada HTA bodies

Patient, family, and other circumstances tied to the need for new medicines may be underrecognized. SPMI patients and families are often marginalized and patient advocates may have fewer resources.	Improving deliberative processes including a broader range of stakeholders (e.g., more clinicians and families) along with better inputs (e.g., through advisory bodies or listening exercises).	HTA bodies
The value of choice and variability of response to medication may be overlooked by HTA bodies using population health/average approaches to assessing outcomes.	HTA bodies could supplement traditional approaches to examining trials with approaches to ascertaining individual value. Manufacturers could go beyond the minimal design in trials posed by regulators to better address variability. Payers and manufacturers and could consider innovative risk-sharing approaches.	HTA bodies Drug manufacturers Public Payers
The prices of new therapies can impact persistence on medication, even with patient co-pays.	Drug companies need to reconsider their pricing model for drugs for SPMI. First dollar coverage models should be considered by private and public insurers, or through product listing agreements.	Drug manufacturers Public and private payers

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Appendix A

AGENDA:

Optimizing care for patients in Canada with severe, persistent mental illness: *an invitational IHE Virtual Roundtable*

Date: Thursday, April 25th, 2024. Time: 9:30 to 11:30 MT/11:30 to 1:30 ET

Welcome and Introductions: (5 minutes) – John Sproule Overview Presentation: (15 minutes) – Don Husereau Facilitated discussion: (All)

Question one: 40 minutes – including reflection back on key points and active seeking response to suggestions raised.

• What key actions do you recommend to accelerate access for Canadian patients to new therapies in this area? (including assessment bodies, public payors, prescribers, patients and manufacturers).

Question Two: 40 minutes – including reflection back on key points.

• What key policy areas outside of medication access merit ongoing engagement and collective strategy development to support this population?

Round robin: Key learnings and final points. (20 minutes).

Invited Participants:

Name	Affiliation	Perspective
Pierre Chue	Alberta Health Services	Clinician
Dave Gallson	Mood Disorders Society of Canada	Patient Representative
Fred Horne	Horne and Associates	Provincial Government
Don Husereau	IHE	NA (meeting facilitator)
Beth Kidd	Health Coalition of Alberta	Patient Representative
Brent Korte	Canadian Mental Health Association	Board Chair – Alberta Division
Heather Logan	Canada's Drug Agency	Health Technology Assessment
Raj Mangal	AbbVie	Drug Manufacturer
Rebeccah Marsh	IHE	Mental Health Policy
Chad Mitchell	Government of Alberta	Provincial Government
Lynda Ravlich	AbbVie	Drug Manufacturer
Sandra Rees	Government of Alberta	Provincial Government
Rubyann Rice	Schizophrenia Society of Alberta	Patient Representative
John Sproule	IHE	NA (meeting facilitator)
David Tano	Alberta Health Services	Clinician
Nancy Zorzi	Nancy Zorzi Communications Inc.	Patient organization
Tim Battle	Health Coalition of Alberta	Patient Representative
Wendy Bonertz	Schizophrenia Society of Alberta	Patient Representative