ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Cognitive Behavioural Therapy for Psychosis: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Schizophrenia is a severe, chronic mental disorder that causes episodes of psychosis with symptoms ranging from delusions to social withdrawal. It is usually treated with medication and psychological care. About 8,000 people, mostly young adults, are newly diagnosed each year in Ontario, and they are at increased risk of having other psychiatric conditions, including substance use disorders, depression, and anxiety, and experiencing homelessness and suicide.

Recent guidelines and quality standards on care for people with schizophrenia recommend a form of psychotherapy called cognitive behavioural therapy (CBT) for psychosis. This therapy is publicly funded in Ontario if provided by a regulated professional such as a psychologist in a government-funded clinic or by a medical doctor. However, many free services have long wait lists or are not locally available.

In this report, we looked at systematic reviews of published studies on CBT for psychosis for adults with schizophrenia (aged 18 years and older) to understand how effective it is in reducing symptoms and helping people function. We then conducted an economic evaluation to estimate what it would cost to publicly fund CBT for psychosis in addition to usual care. We also interviewed people affected by schizophrenia to understand the impact of the condition and their treatment experiences.

What Did This Health Technology Assessment Find?

When added to usual care, CBT for psychosis can significantly reduce people's psychotic symptoms, but the systematic reviews we reviewed did not convincingly show that it improves their risk of relapse, social function, or quality of life. Less evidence was available on the best format or delivery model for this therapy. No systematic reviews compared types of providers or online versus in-person sessions.

People with lived experience spoke positively about CBT for psychosis but said geographic and financial barriers made it hard to access. Our economic analyses showed adding CBT for psychosis to usual care for adults with schizophrenia in Ontario probably represents good value for money. Assuming CBT for psychosis is provided to 20% of eligible patients in the first year and reaches 100% by year 5, publicly funding this therapy would cost an extra $15 million over the next 5 years if the therapy were provided by regulated nonphysicians (such as psychologists), or about $35 million if provided by psychiatrists. About 110 nonphysician therapists or 150 physicians trained in CBT for psychosis would be needed.

Published October 2018
Volume 18, Number 5

Ontario
Health Quality Ontario

HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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We are grateful to the people who shared their experiences with us for this report. We are also grateful to the following clinical and health economic experts for their advice in preparing this health technology assessment: Faye Doell, Centre for Addiction and Mental Health; Joel Goldberg, York University; Nick Kates, McMaster University; Sean Kidd, Centre for Addiction and Mental Health; Muhammad Mamdani, St. Michael's Hospital; Farooq Naeem, Centre for Addiction and Mental Health; and David Tannenbaum, Mount Sinai Hospital, Toronto.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Citation

Health Quality Ontario. Cognitive behavioural therapy for psychosis: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2018 Oct;18(5):1–141. Available from: http://www.hqontario.ca/evidence-to-improve-care/journal-ontario-health-technology-assessment-series

ABSTRACT

Background

Cognitive behavioural therapy (CBT) for psychosis is a distinct type of psychotherapy that has been recommended together with antipsychotic drugs and comprehensive usual care in the management of schizophrenia, a complex mental health disorder associated with a high economic and societal burden. The objectives of this report were to assess the effectiveness, harms, cost-effectiveness, and lived experience of CBT for psychosis in improving outcomes for adults with a primary diagnosis of schizophrenia.

Methods

We performed literature searches on March 28 and April 5, 2017, and undertook a qualitative synthesis of systematic reviews of the clinical and economic literature comparing CBT for psychosis with any comparator interventions (e.g., usual care, waitlist control, or pharmacotherapy) in adults with a diagnosis of schizophrenia as defined by any criteria (including related disorders such as schizoaffective disorder).

We developed an individual-level state-transition probabilistic model for a hypothetical cohort of adults aged 18 years and older starting with first-episode psychosis. We compared three strategies: usual care, CBT for psychosis by physicians, and CBT for psychosis by regulated nonphysician therapists. The CBT was provided in person together with usual care including pharmacotherapy: 16 structured sessions (individual or group) for first-episode psychosis and 24 individual sessions for relapse or treatment-resistant disease. We calculated incremental cost-effectiveness ratios (ICERs) over 5 years using the Ontario Ministry of Health and Long-Term Care perspective and a discount rate of 1.5%. We also estimated the 5-year budget impact of publicly funding CBT for psychosis in Ontario.

In addition, we interviewed 13 people with lived experience of schizophrenia and psychosis about their values and preferences surrounding CBT and other treatments.

Results

CBT for psychosis compared with usual care significantly improved overall psychotic symptoms (standard mean difference [SMD] −0.33, 95% confidence interval [CI] −0.45 to −0.21), positive symptoms (e.g., hallucinations) (SMD −0.34, 95% CI −0.58 to −0.10), auditory symptoms (SMD 0.39, 95% CI not reported, $P < .005$), delusions (SMD 0.33, 95% CI not reported, $P < .05$) and negative symptoms (e.g., blunt affect) (SMD −0.32, 95% CI −0.59 to −0.04) at end of treatment. No significant differences were observed for social function, distress associated with psychosis, relapse, or quality of life.

Compared with any control, CBT for psychosis significantly improved overall psychotic symptoms, positive symptoms, auditory hallucinations, delusions, and negative symptoms. Compared with other forms of therapy, CBT for psychosis showed inconsistent results at end of treatment for overall psychotic symptoms, positive symptoms, auditory hallucinations, and delusions. In people with first-episode psychosis, CBT for psychosis was not significantly more effective for the prevention of relapse when compared with other forms of therapy or usual care (odds ratio [OR] 1.11, 95% CI 0.63–1.95 and OR 1.15, 95% CI 0.65–2.04, respectively).

Low-intensity CBT for psychosis (fewer than 16 face-to-face sessions) compared with any type of treatment significantly improved overall psychotic symptoms and social function at follow-up (SMD −0.40, 95% CI −0.74 to −0.06 and SMD −0.57, 95% CI −0.81 to −0.33, respectively).

In the cost-utility analysis, CBT for psychosis provided by nonphysician therapists compared with usual care was associated with increases in both quality-adjusted life-years (mean 0.1159 QALYs, 95% credible interval [CrI] 0.09–0.14) and costs (mean $2,494, 95% CrI $1,472–$3,544), yielding an ICER of $21,520 per QALY gained. CBT for psychosis provided by physicians was dominated because it was equally effective but more expensive (mean $2,976, 95% CrI $2,822–$3,129; ICER of CBT for psychosis vs. usual care: $47,196/QALY gained).

Assuming a 20% increase in access per year (from 0% at baseline to 100% in year 5), we estimated the total 5-year net budget impact of publicly funding CBT for psychosis would be about $15.2 million for nonphysician providers and about $35.4 million if provided by psychiatrists. It is estimated that by the year 2021, approximately 110 nonphysician therapists or 150 physicians would be needed to provide CBT for psychosis to more than 12,000 adults with schizophrenia (including about 8,500 incident cases) in Ontario.

People with schizophrenia and their family members reported positive experiences with CBT for psychosis. They felt it provided effective tools to help manage their schizophrenia but stressed that it was only effective in conjunction with medication to control psychotic episodes and overcome a patient's denial of illness. Geographic and financial barriers have restricted access to this psychotherapy.

Conclusions

Compared with usual care or any control, CBT for psychosis significantly improved psychotic symptoms, based on evidence of moderate to adequate quality; no significant improvements were observed for social function, relapse, or quality of life outcomes. People affected by schizophrenia reported that CBT for psychosis was valuable in conjunction with antipsychotic medication but that access to this type of psychotherapy is limited. Adding CBT for psychosis to usual care in the management of adult schizophrenia probably represents good value for money in Ontario. Depending on the type of provider, therapy format, and rate of access, the net budget impact to Ontario's publicly funded health system would likely be between $15 million to $35 million over the next 5 years.

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OBJECTIVE

This health technology assessment looked at the effectiveness, harms, cost-effectiveness, potential budget impact, and patient experiences of cognitive behavioural therapy for treating psychosis in adults with a primary diagnosis of schizophrenia (including related disorders such as schizoaffective disorder).

BACKGROUND

Health Condition

Schizophrenia is a complex mental health disorder that usually presents with a first episode of psychosis (a loss of contact with external reality) in people between 16 and 30 years of age. Symptoms of schizophrenia are often categorized as either positive or negative. Positive symptoms include hallucinations, delusions, and/or disturbed behaviour, while negative symptoms include blunted affect (reduced emotional expression) and lack of motivation. These symptoms can also appear in combination with mood disorders such as depression or mania, in a condition called schizoaffective disorder. People with schizophrenia often experience social or occupational dysfunction and struggle with self-care.[1]

Schizophrenia is a life-long condition, and treatment generally involves a combined approach of medication and psychosocial interventions (interpersonal or informational techniques that aim to help people understand and function with their condition). People typically experience an at-risk period, called the prodromal period, characterized by difficulties in memory and attention, social withdrawal, and unusual or uncharacteristic behaviour.[1] The prodromal period is typically followed by an acute phase marked by positive symptoms. In the early stages of schizophrenia, people often experience repeated and worsening symptoms, and the potential for relapse after initial treatment is high. Around 80% of people with schizophrenia will relapse within 5 years of a treated first episode; this is partly due to discontinuing medication.[2]

Clinical Need and Target Population

The prevalence of schizophrenia among adults in Ontario (ages 18 to 64 years) is 11.5 per 1,000 people.[3] The prevalence is greater in men.[4]

People with schizophrenia have a life expectancy 15 to 20 years shorter than the general population; most of these premature deaths are due to cardiovascular and chronic respiratory diseases.[5] Between 1993 and 2012 in Ontario, people with schizophrenia experienced 3 times greater mortality rates, compared with the general population, even after adjustment for sociodemographic factors.[6] Cause-specific age- and sex-standardized mortality rates were greater for those with schizophrenia, with circulatory disease accounting for most deaths.[6] Among those with schizophrenia, relative declines throughout the 20 years were greater for unnatural deaths but smaller for deaths from circulatory disease.[6]

People with schizophrenia are also at an increased risk of substance use (including smoking), homelessness, and unemployment.[1]

Current Treatment Options

Treatment of schizophrenia is complex and involves medications and inpatient, outpatient and community mental health services such as psychoeducation (helping people understand the

illness), family therapy, and social/vocational interventions which aim to facilitate social interactions and coach practical applications of skills learned.[7-12]

Antipsychotic drugs are the primary treatment and are effective in reducing symptoms and preventing relapses. In the acute phase of schizophrenia, the goal of pharmacotherapy (generally up to 8 weeks from the beginning of a psychotic episode) is to reduce the severity of psychotic thoughts and behaviours. Most people who will improve with medication will see the most rapid improvement within the first 2 weeks.[13]

People who recover from an acute psychotic episode tend to reach a stabilizing or maintenance phase where psychotic thoughts and behaviours are more controlled. The aim of treatment in the maintenance phase is to minimize symptoms and functional impairments, avoid relapses, and promote recovery. However, a substantial proportion of people with schizophrenia—up to 40%—respond poorly to antipsychotic drugs and continue to experience moderate to severe psychotic symptoms. This may happen, in part, because many people find it hard to stay on antipsychotic drugs long term due to their challenging side effects.[1]

Antipsychotic drugs tend to be grouped into two categories—first-generation (e.g., haloperidol, chlorpromazine) and second-generation (SGAs, e.g., risperidone, quetiapine, olanzapine, aripiprazole)—although broadly grouping them this way has been challenged.[14] Second-generation antipsychotics are often recommended by clinical guidelines because, compared to the first-generation antipsychotics, they are associated with lower intensities of intolerable side effects such as sedation or extrapyramidal symptoms (uncomfortable tremors, spasms, and stiffness, similar to Parkinson disease). However, some SGAs (e.g., olanzapine) are associated with high risk of weight gain and metabolic syndrome, potentially leading to severe complications such as diabetes and cardiovascular disease.[9-11,15-20]

Other drugs such as anticonvulsants, mood stabilisers, anticholinergics, antidepressants, and benzodiazepines are sometimes used in combination with antipsychotic drugs to help people with schizophrenia better achieve treatment goals.[1]

Health Service Under Review

Description and Indications

Cognitive behavioural therapy (CBT) for psychosis is a form of psychotherapy that engages the person in examining and challenging their psychotic experiences and developing coping strategies to manage symptoms. This therapy is recommended for use alongside antipsychotic drugs and comprehensive usual care (case management and community mental health services).[8,10,21,22] To help people improve their social and occupational dysfunctions, CBT for psychosis is often combined with motivational and vocational interventions.[23-26]

The goals of CBT for psychosis are to reduce the occurrence of symptoms, the distress associated with them, and/or the degree to which symptoms interfere with the person's functioning and quality of life. The cognitive components of CBT for psychosis aim to teach people with schizophrenia to identify and monitor their thoughts and assumptions in specific situations and to evaluate and correct these thoughts and assumptions against objective external evidence and actual circumstances.[22] The behavioural components of the therapy aim to increase coping skills and reduce problematic behaviours.

CBT for psychosis represents a distinct type of psychotherapy.[27] While it shares some generic components of CBTused to treat depression and anxiety, it also has specific components targeted at the broader range of psychotic symptoms and social challenges that affect people with schizophrenia.[22,27] CBT for psychosis is a structured therapy with four core components or stages[22,27]: (1) creation of the therapeutic alliance (establishing rapport between patient and clinician and agreeing on treatment goals); (2) education and normalization of the patient's psychotic symptoms (helping the patient understand the illness); (3) case formulation and treatment plan (assessing the patient's specific symptoms and developing targeted approaches to help alleviate them); and (4) a closing phase to prevent relapse and promote continued recovery.

According to the 2017 Canadian treatment guidelines, CBT for psychosis is recommended for people with schizophrenia who do not adequately respond to antipsychotic medication and have persistent symptoms including anxiety and depression.[28] Therefore, it is mainly offered to people with established or treatment-resistant disease.[24,26,28-31] However, people in early stages of psychosis may also be appropriate for CBT for psychosis, particularly to alleviate the impact of depression, anxiety, and substance use disorders that often occur in first-episode psychosis.[32]

Training and Competency of Providers

Providing CBT for psychosis requires specific advanced training.[22] In general, this therapy is delivered by physicians (e.g., psychiatrists) or regulated nonphysician providers (e.g., clinical psychologists) with significant training and experience.[22,33]

In Ontario, for example, the College of Psychologists of Ontario specifies these minimum requirements for psychologists to provide this therapy unsupervised:

- A master's degree in psychology with 4 years of practice and at least one additional year of formal supervised experience in CBT for psychosis, or
- A doctoral degree in psychology with a one-year internship in CBT for psychosis and at least one additional year of formal supervised experience in this therapy

For CBT for psychosis to succeed, the person with schizophrenia must actively engage in the therapy, and establishing a good therapeutic alliance between the patient and clinician during the first stage of therapy is extremely important.[22,27] Goldsmith et al[34] showed that inadequate therapeutic alliance due to clinicians' incompetence was detrimental for people with schizophrenia. The 2017 Canadian treatment guidelines recommend that CBT for psychosis be delivered by appropriately trained therapists who follow established, effective protocols including regular supervision.[28]

Format and Duration

Cognitive behavioural therapy for psychosis can be provided in individual or group settings. The individual format is promoted in the UK guidelines, as no randomized controlled trials have directly compared group and individual CBT for psychosis.[28] On the other hand, a number of studies, many conducted in North America, have suggested benefits of group CBT for psychosis: normalizing the patient's experience (through seeing that other people have had similar experiences), increasing self-esteem, and reducing social isolation (related to social anxiety or stigma).[22,33,35,36] Group CBT for psychosis typically includes 8 participants with 2 clinicians delivering the therapy.[22]

CBT for psychosis is often delivered using a structured manual that breaks down phases of the therapy into specific sessions.[37-40] Recent guidelines recommend that a course of CBT for psychosis should be a minimum of 16 sessions.[28] In practice, the duration of therapy varies from 9 to 12 months with 12 to 36 sessions in the initial course of therapy (typically 45- to 60-minute weekly sessions) and an additional 2 to 4 booster sessions aimed at improving recovery and preventing relapse.[10,22,28]

Brief or low-intensity CBT for psychosis involves 6 to 10 sessions occurring over less than 4 months. It has been suggested as a way of increasing access to this treatment.[41] Low-intensity CBT for psychosis tends to be more skills-based (focused on specific symptoms or areas of difficulty), whereas a full course of therapy is more formulation-driven (requires a more thorough understanding of the person) and allows for a more comprehensive treatment plan for people with first-episode psychosis and recurrent disease (expert consultant, personal communication, Oct 2017).

Ontario Context

Numerous clinical guidelines[8-10,19,28] and Health Quality Ontario's quality standard, *Schizophrenia: Care for Adults in Hospitals*,[12] have recommended the use of CBT for psychosis as part of the complex treatment of schizophrenia. However, access to this therapy is limited in Ontario.

In Ontario, CBT for psychosis, like other forms of CBT, is typically delivered by trained clinical psychologists or trainees under their supervision, or by other regulated mental health therapists. This therapy may be publicly funded when provided by these regulated professionals in government-funded hospitals, clinics, or agencies. It is publicly funded through the Ontario Health Insurance Plan (OHIP) only if delivered by a psychiatrist or other CBT-trained physician.

Fees for psychologists in private practice with CBT training may be partially covered by private or workplace insurance. However, given that schizophrenia often prevents people from working, few people who need CBT for psychosis have private insurance coverage or can afford private therapy. Most receive income assistance from the Ontario Disability Support Program.

The reimbursement context in other Canadian provinces and territories is similar to that of Ontario.

CLINICAL EVIDENCE

Research Questions

- What are the effectiveness and harms of cognitive behavioural therapy (CBT) for psychosis in improving outcomes for adults with a primary diagnosis of schizophrenia (including related disorders such as schizoaffective disorder)?
- What are the effectiveness and harms of brief or low-intensity CBT?
- What are the effectiveness and harms of CBT for psychosis provided by physician versus nonphysician providers?
- What are the effectiveness and harms of individual versus group CBT for psychosis?
- What are the effectiveness and harms of online versus in-person CBT for psychosis?

Methods

We developed research questions in consultation with health care providers, clinical experts, and other health system stakeholders.

Literature Search

We performed a literature search on March 28, 2017, to retrieve studies published from inception to the search date. We used the Ovid interface to search the following databases: MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, National Health Service Economic Evaluation Database (NHSEED); and we used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The search strategies were developed using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[42] We created database auto-alerts in MEDLINE, Embase, PsycINFO, and CINAHL and monitored them for the duration of the assessment period.

We also performed targeted grey literature searching of health technology assessment agency sites and PROSPERO, an international database of prospectively registered systematic reviews. See Appendix 1 for our literature search strategies, including all search terms.

Literature Screening

A single reviewer reviewed the abstracts for inclusion based on the study title and abstract. We obtained full-text copies of studies that appeared to meet the inclusion criteria or where a decision could not be made based solely on title or abstract. Articles that cited or were cited by the included studies were also screened to identify any further relevant studies not identified through the search.

Types of Studies

We undertook an overview of existing reviews and, thus, eligible studies were restricted to those that employed a systematic review design. We considered publications to be systematic reviews if they (1) included a clearly specified review question and eligibility criteria, (2) undertook a reproducible search of two or more electronic literature databases, and (3) assessed and

documented the quality of the included studies. Review articles that did not meet all three criteria were excluded. Eligibility was limited to reviews available in English.

Types of Participants

We included reviews of adults with a diagnosis of schizophrenia as defined by any criteria (including related disorders such as schizoaffective disorder). Reviews that focused on people with prodromal symptoms (people at risk of developing first-episode psychosis) were excluded.

Types of Interventions

We included reviews that assessed all forms of CBT for psychosis (e.g., individual, group, brief, standard, or online). Reviews considering self-help interventions were excluded.

Any comparator interventions were eligible for inclusion (e.g., usual care, pharmacotherapy, or waitlist control; in waitlist control, some study participants are assigned to a waiting list and receive the intervention after the active treatment group).

Types of Outcomes Measures

Included reviews needed to have measured at least one of the following outcomes:

- Overall psychotic symptoms
- Positive symptoms
- Negative symptoms
- Distress associated with psychosis
- Adverse effects
- Relapse
- Readmission to hospital
- Quality of life
- Satisfaction with treatment
- Suicidality
- Employment
- Disability
- Death

Data Extraction

We extracted relevant data using a data form to collect information about:

- Source (i.e., author/year, objectives, country of publication)
- Search details (i.e., databases/sources searched, range (years) of search, types of studies included, language restrictions, geographical scope, health care settings included)
- Review participants
- Interventions (i.e., general description of interventions and comparators)
- Outcomes

- Review authors' assessment of overall quality of the evidence (i.e., appraisal instruments used, appraisal rating)
- Analysis and results (i.e., method of analysis, number of studies included, results/findings, heterogeneity)

Where the same review was published more than once (e.g., Cochrane Collaboration review and subsequent update), only the updated version was included. We also contacted authors of the reviews to provide clarification as needed.

Evidence Synthesis

To avoid the risk of double-counting evidence where multiple systematic reviews contained the same primary studies, we undertook a narrative summary of the effect of CBT for psychosis on outcomes.

Critical Appraisal

Assessment of Methodological Quality of Included Reviews

We used the Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool to perform a critical appraisal of the methodological quality of the reviews.[43] See Appendix 2, Table A1, for details of the AMSTAR analysis.

Assessment of Risk of Bias of Included Reviews

We used the Risk of Bias in Systematic Reviews (ROBIS) tool to specifically assess the risk of bias of the included reviews.[44] This is a tool that assesses four key review domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. See Appendix 2, Table A2, for details of the ROBIS assessment.

Assessment of the Quality of the Evidence in Reviews

We assessed the quality of the evidence within the included reviews by extracting the review authors' GRADE (Grading of Recommendations Assessment, Development, and Evaluation) ratings, if sufficient information was provided. If other quality measures were used by the review authors in the included reviews, these were reported.

Expert Consultation

Starting in March 2017, we solicited expert consultation on the use of CBT for psychosis. Experts consulted included health care providers in the specialty areas of psychotherapy and psychiatry. The role of the expert advisors was to contextualize the evidence and provide advice on the use of CBT for psychosis. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 1,420 citations published from inception to March 28, 2017, with an additional 4 citations identified from a search of health technology assessment websites. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant

articles. We obtained the full texts of 78 articles for further assessment. Thirteen studies met the inclusion criteria. Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[45] Appendix 3 lists the studies we excluded after full-text review, with the primary reason for exclusion.

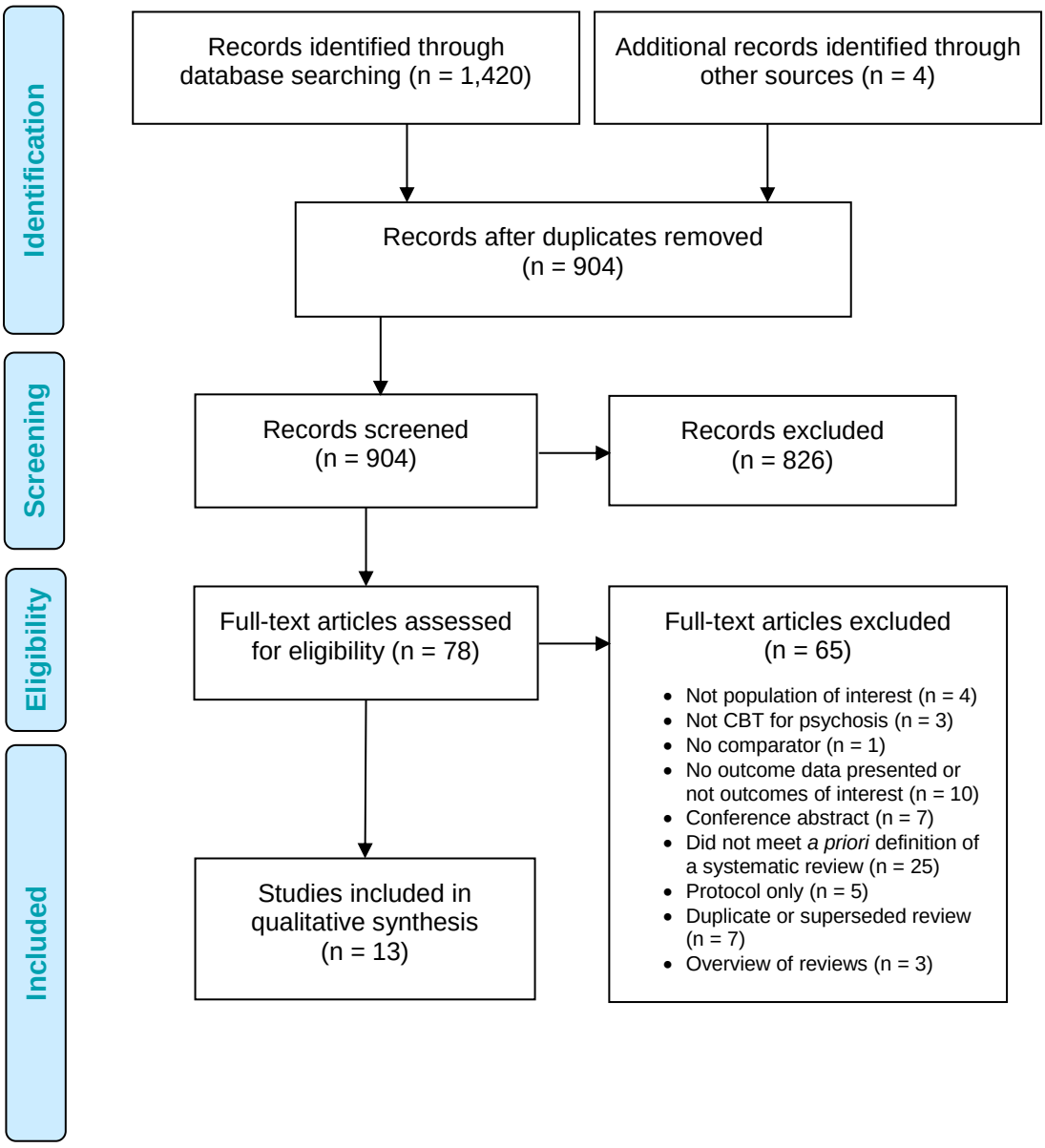

Figure 1: PRISMA Flow Diagram – Clinical Search Strategy

Source: Adapted from Moher et al, 2009.[45]

We identified 13 systematic reviews that reported data on a range of outcomes when CBT for psychosis was compared with usual care, another form of psychotherapy, or any control (usual care or another form of psychotherapy).[46-58] All the included systematic reviews restricted their searches to randomized controlled trials (RCTs) and, in all cases, CBT for psychosis was delivered in conjunction with antipsychotic drugs. Two systematic reviews focused specifically

on people who had experienced their first episode of psychosis.[46,52] Characteristics of the included systematic reviews are summarized in Appendix 4, Table A3.

Cognitive Behavioural Therapy for Psychosis Compared With Usual Care

Four systematic reviews compared CBT for psychosis with usual care on a range of outcomes.[47,51,55,58] Usual care was generally described as treatment with antipsychotic drugs and could include supportive interventions. The included RCTs took place in either a hospital or community setting, and the CBT was delivered in either a group or individual setting.

Full results for CBT for psychosis compared with usual care can be found in Table 1.

Overall Symptoms

One systematic review reported a pooled effect size for overall symptoms favouring CBT for psychosis at the end of treatment, compared with usual care.[58] Overall symptoms were calculated based on total scores on general psychiatric scales that rated not just positive and negative symptoms but also other symptoms. Scales used included the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), the Comprehensive Psychopathology Rating Scale (CPRS), and the Hopkins Psychiatric Rating Scale.

Positive Symptoms

Two systematic reviews reported a pooled effect size for positive symptoms favouring CBT for psychosis at the end of treatment, compared with usual care.[47,58] The scales used in studies reviewed by Jauhar et al[58] included positive symptom subscales of the PANSS, BPRS, the Krawiecka (Manchester) scale, the Schedule for the Assessment of Positive Symptoms (SAPS), and the Psychotic Symptom Rating Scales (PSYRATS). Scales used in studies reviewed by Baandrup et al[47] included PANSS positive, SAPS, and BPRS positive.

One systematic review reported a nonsignificant pooled effect size for positive symptoms of psychosis at the end of follow-up (minimum 4 to 6 months).[47]

Auditory Hallucinations

One systematic review reported a pooled effect size for auditory hallucinations favouring CBT for psychosis at the end of treatment, compared with usual care.[55] Scales used in studies reviewed by van der Gaag et al[55] included PSYRATS, the MacArthur-Maudsley Delusions Assessment Schedule (MMDAS), the Peters Delusion Inventory (PDI), the Comprehensive Assessment of Psychiatric Symptoms (CPRS), and the Beliefs about Voices Questionnaire (BAVQ-R).

Delusions

One systematic review by van der Gaag et al[55] reported a pooled effect size for delusions favouring CBT at the end of treatment, compared with usual care. Scales used by studies in the meta-analysis by van der Gaag et al[55] included PSYRATS, MMDAS, PDI, CPRS, and BAVQ-R.

Negative Symptoms

Three systematic reviews by Lutgens et al,[51] Baandrup et al,[47] and Jauhar et al[58] reported a pooled effect size for negative symptoms favouring CBT for psychosis at the end of treatment,

compared with usual care. Lutgens et al[51] reported negative symptom outcomes based on a valid and reliable negative symptom measurement, e.g., Scale for Assessment of Negative Symptoms (SANS) and the Negative Symptom subscale of PANSS. Baandrup et al[47] reported the scales used to assess symptom outcome were PANSS negative, SANS, BPRS negative, and Brief Rating Instrument for Assessment of Negative Symptoms Scale (BRIANS). Jauhar et al[58] reported the negative symptom subscale of the PANSS, the SANS, the BPRS negative factor, and a negative symptoms scale derived from the CPRS and from the Krawiecka (Manchester) scale.

Baandrup et al[47] reported a nonsignificant difference in negative symptoms at the end of follow-up (pooled effect size, CBT compared with usual care).

Social Function

Baandrup et al[47] reported a nonsignificant difference in social function at the end of treatment (pooled effect size, CBT compared with usual care). Scales used included Social and Occupational Functioning Assessment Scale (SOFAS), Social Provisions Scale (SPS), Social Functioning Scale (SFS), Global Assessment Scale (GAS), Global Functioning Scale (GAF).[47]

Distress Associated With Psychosis

Baandrup et al[47] reported no significant difference between CBT and usual care for distress associated with psychosis at the end of treatment. The scale used to assess this outcome was PSYRATS (hallucinations).[47]

Relapse

Baandrup et al[47] reported a nonsignificant difference in relapse at the end of treatment (pooled effect size, CBT compared with usual care).

Quality of Life

Baandrup et al[47] reported a nonsignificant difference in quality of life at the end of treatment with CBT compared with usual care (pooled effect size). Scales used in the studies within the meta-analysis by Baandrup et al[47] included Quality of Life Scale (QLS), World Health Organization's Quality of Life scale (WHOQOL), and Quality of Life Enjoyment and Satisfaction Questionnaire (QSQ).

Days in Hospital

Baandrup et al[47] reported a nonsignificant difference in the number of days in hospital at the end of treatment with CBT compared with usual care (pooled effect size).

Table 1: Summary of Results, CBT for Psychosis Compared With Usual Care

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
Overall psychotic symptoms (end of treatment)			
Jauhar et al, 2014[58]	21 studies	SMD −0.33, 95% CI −0.45 to −0.21, *P* = NR Heterogeneity: NR	NR
Positive symptoms (end of treatment)			
Baandrup et al, 2016[47]	15 studies / 1,078 participants	SMD −0.34, 95% CI −0.58 to −0.10, *P* = .006 Heterogeneity: I^2 = 72%	GRADE: moderate
Jauhar et al, 2014[58]	19 studies	SMD −0.31, 95% CI −0.45 to −0.17, *P* = NR Heterogeneity: NR	NR
Positive symptoms (follow-up)			
Baandrup et al, 2016[47]	10 studies / 892 participants	SMD −0.09, 95% CI −0.38 to 0.19, *P* = .52 Heterogeneity: I^2 = 74%	GRADE: low
Auditory hallucinations (end of treatment)			
van der Gaag et al, 2014[55]	9 studies / 558 participants	SMD 0.39, 95% CI NR, *P* < .005 (favours CBT) Heterogeneity: I^2 = 0	Mean CTAM score = 65 (range 34–93)
Delusions (end of treatment)			
van der Gaag et al, 2014[55]	6 studies / 480 participants	SMD 0.33, 95% CI NR, *P* < .05 (favours CBT) Heterogeneity: I^2 = 51.2%	Mean CTAM score = 74 (range 48–93)
Negative symptoms (end of treatment)			
Lutgens et al, 2017[51]	11 studies	SMD −0.43, 95% CI −0.55 to −0.30, *P* = NR Heterogeneity: NR	NR
Baandrup et al, 2016[47]	18 studies / 1,214 participants	SMD −0.32, 95% CI −0.59 to −0.04, *P* = .02 Heterogeneity: I^2 = 80%	GRADE: moderate
Jauhar et al, 2014[58]	20 studies	SMD −0.17, 95% CI −0.33 to −0.02, *P* = NR Heterogeneity: NR	NR
Negative symptoms (follow-up)			
Baandrup et al, 2016[47]	12 studies / 1,011 participants	SMD −0.08, 95% CI −0.30 to 0.13, *P* = .44 Heterogeneity: I^2 = 60%	GRADE: very low
Social function (end of treatment)			
Baandrup et al, 2016[47]	8 studies / 575 participants	SMD −0.07, 95% CI −0.23 to 0.10, *P* = .44 Heterogeneity: I^2 = 0%	GRADE: moderate
Distress associated with psychosis (end of treatment)			
Baandrup et al, 2016[47]	6 studies / 236 participants	MD 0.22, 95% CI −0.84 to 1.28, *P* = .68 Heterogeneity: I^2 = 64%	GRADE: low
Relapse (end of treatment)			
Baandrup et al, 2016[47]	4 studies / 363 participants	RR 0.80, 95% CI 0.48 to 1.32, *P* = .38 Heterogeneity: I^2 = 35%	GRADE: low
Quality of life (end of treatment)			
Baandrup et al, 2016[47]	4 studies / 297 participants	SMD 0.03, 95% CI −0.32 to 0.38, *P* = .86 Heterogeneity: I^2 = 35%	GRADE: low
Days in hospital (end of treatment)			
Baandrup et al, 2016[47]	4 studies / 425 participants	MD −10.64, 95% CI −32.14 to 10.86, *P* = .33 Heterogeneity: I^2 = 94%	GRADE: low

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; CTAM, Clinical Trials Assessment Measure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NA, not applicable; NR, not reported; RR, relative risk; SMD, standardized mean difference.

Cognitive Behavioural Therapy for Psychosis Compared With Other Psychotherapy

Six systematic reviews compared CBT for psychosis with other psychotherapy such as supportive counselling, psychoeducation, or cognitive remediation.[49-51,54,55,58] Individuals were treated with antipsychotic drugs in both the treatment and control arms of the included RCTs, and CBT for psychosis was delivered in either a group or individual setting. Only one systematic review restricted the setting of included primary studies to the community.[50]

Table 2 shows full results for the systematic reviews of CBT for psychosis compared with other psychotherapy.

Important or Reliable Change in General Mental State

One systematic review reported a nonsignificant difference in the pooled summary estimate of important or reliable change in general mental state at the end of treatment and at the end of follow-up, for people receiving CBT for psychosis compared with other psychotherapy.[49]

The definitions of important or reliable change varied between the included trials.[49] For example, one trial defined clinically significant change as greater than two standard deviations on PANSS global score and a statistically significant Reliable Change Index.[49] Another study defined important or reliable change as a clinically significant reduction of positive symptoms, which is a 20% reduction in PANSS positive factor score, and another defined important or reliable change as partial or full remission of symptoms without further episode.[49]

Overall Symptoms

One systematic review reported a nonsignificant difference in overall symptoms at the end of treatment with CBT compared with other psychotherapy (pooled effect size).[58] Overall symptoms were calculated based on total scores on general psychiatric scales that rated not just positive and negative symptoms but also other symptoms. Scales used included the PANSS, BPRS, CPRS, and the Hopkins Psychiatric Rating Scale.

A second systematic review reported a pooled effect size for overall symptoms favouring CBT compared with other psychotherapy at the end of treatment.[54] The results continued to be significant when studies with high risk of bias were excluded from the pooled summary estimate but lost significance when studies with a low risk and any risk of bias were excluded.[54] Symptom outcomes were measured using a variety of validated scales.

Positive Symptoms

One systematic review reported a nonsignificant difference in positive symptoms at the end of treatment with CBT compared with other psychotherapy (pooled effect size).[58] The scales used by studies reviewed by Jauhar et al[58] included positive symptom subscales of the PANSS, BPRS, the Krawiecka (Manchester) scale, SAPS, and PSYRATS.

A second systematic review reported a pooled effect size for positive symptoms favouring CBT compared with other psychotherapy at the end of treatment.[54] The results continued to be significant when studies with high, low, and any risk of bias were excluded from the pooled summary estimate.[54]

A third systematic review reported a nonsignificant pooled mean difference in positive symptoms at the end of treatment for people receiving CBT compared with other psychotherapy

(using the positive symptom subscale of the PANSS) and a significant mean difference in positive symptoms favouring CBT at the end of follow-up.[49]

Auditory Hallucinations

One systematic review reported a pooled effect size for auditory hallucinations favouring CBT for psychosis compared with other psychotherapy at the end of treatment.[55] Scales used by studies in the review by van der Gaag et al[55] included PSYRATS, MMDAS, PDI, CPRS, and the BAVQ-R.

Two other systematic reviews reported a nonsignificant mean difference in auditory hallucinations between CBT for psychosis and other psychotherapy at the end of treatment and at the end of follow-up.[49,50] Jones et al[49] used the hallucinations subscale of the PSYRATS to report results, and Kennedy et al[50] used the PANSS positive subscale score.

Delusions

One systematic review reported a nonsignificant difference in delusions at the end of treatment with CBT for psychosis compared with other psychotherapy (pooled effect size).[55] Scales used within the meta-analysis by van der Gaag et al[55] included PSYRATS, MMDAS, PDI, CPRS, and BAVQ-R.

A second systematic review reported a significant mean difference at the end of treatment, favouring CBT for psychosis compared with other psychotherapy. However, this difference became nonsignificant at the end of follow-up.[49] The scale reported by Jones et al[49] was the delusions subscale of the PSYRATS.

Negative Symptoms

Four systematic reviews reported a nonsignificant difference between CBT and other psychotherapy in negative symptoms at the end of treatment and at the end of follow-up.[49,51,54,58] Lutgens et al[51] and Turner et al[54] reported negative symptom outcomes based on a valid and reliable negative symptom measurement (e.g., SANS and PANSS). Jauhar et al[58] reported the negative symptom subscale of PANSS, SANS, the BPRS negative factor, and a negative symptoms scale derived from the CPRS and from the Krawiecka (Manchester) scale. Jones et al[49] reported outcomes on the Negative Symptom subscale of the PANSS.

Social Function

One systematic review reported a nonsignificant difference between CBT and other psychotherapy in social function at the end of treatment and at the end of follow-up.[49] The scale reported in the primary study was the SFS.[49]

Relapse

One systematic review reported a nonsignificant difference in relapse at the end of treatment and at the end of follow-up for CBT compared with other psychotherapy.[49] Jones et al[49] noted that the different studies used varied criteria for relapse. For example, one study defined relapse as the “re-emergence of or significant deterioration in positive psychotic symptoms of at least moderate degree persisting for at least 2 weeks,” whereas another study defined relapse as “a rating of at least 5 and a 2-point increase compared with the previous assessment in at least one of the items of the Positive Syndrome Subscale of the PANSS.”[49]

Quality of Life

One systematic review reported a nonsignificant difference in long-term quality-of-life scores (EuroQoL, 24 months) for CBT compared with other psychotherapy.[49]

Rehospitalization

One systematic review reported no significant reduction in rehospitalization either in the short or long term for people who received CBT compared with those receiving other psychotherapy.[49]

Adverse Events

One systematic review reported no significant difference in adverse events between people who received CBT and those who received other psychotherapy.[49]

Death

One systematic review reported no significant difference in deaths for people who received CBT compared with those receiving other psychotherapy.[49]

Table 2: Summary of Results, CBT for Psychosis Compared With Other Psychotherapy

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
Important or reliable change in general mental state (end of treatment)			
Jones et al, 2012[49]	2 studies / 99 participants	RR 0.84, 95% CI 0.40 to 1.75, *P* = .64 Heterogeneity: I^2 = 76%	NR
Important or reliable change in general mental state (at follow-up)			
Jones et al, 2012[49]	4 studies / 244 participants	RR 0.91, 95% CI 0.77 to 1.08, *P* = .28 Heterogeneity: I^2 = 0%	GRADE: very low
Overall psychotic symptoms (end of treatment)			
Jauhar et al, 2014[58]	9 studies	SMD −0.32, 95% CI −0.74 to 0.09, *P* = NR Heterogeneity: NR	NR
Turner et al, 2014[54]	22 studies	SMD 0.16, 95% CI 0.04 to 0.28, *P* < .05 (favours CBT) Heterogeneity: I^2 = 12% *Excluding high risk of bias (18 studies)* SMD 0.12, 95% CI 0.00 to 0.23, *P* < .05 Heterogeneity: I^2 = 0% *Excluding low risk of bias (15 studies)* SMD 0.10 95% CI −0.03 to 0.22, *P* = NR Heterogeneity: I^2 = 0% *Excluding any risk of bias (13 studies)* SMD 0.11, 95% CI −0.02 to 0.24, *P* = NR Heterogeneity: I^2 = 0%	Subgroup analysis undertaken based on risk of bias
Positive symptoms (end of treatment)			
Jauhar et al, 2014[58]	10 studies	SMD −0.24, 95% CI −0.54 to 0.06, *P* = NR Heterogeneity: NR	NR
Turner et al, 2014[54]	17 studies	SMD 0.16, 95% CI 0.04 to 0.28, *P* < .05 (favours CBT) Heterogeneity: I^2 = 0% *Excluding high risk of bias (15 studies)* SMD 0.14, 95% CI 0.02 to 0.27, *P* < .05 Heterogeneity: I^2 = 0%	Subgroup analysis undertaken based on risk of bias

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
		Excluding low risk of bias (12 studies) SMD 0.15, 95% CI 0.02 to 0.28, *P* < .05 Heterogeneity: I^2 = 0% *Excluding any risk of bias (11 studies)* SMD 0.14, 95% CI 0 to 0.27, *P* < .05 Heterogeneity: I^2 = 0%	
Jones et al, 2012[49]	7 studies / 477 participants	MD −0.67, 95% CI −1.46 to 0.13, *P* = .10 Heterogeneity: I^2 = 47%	NR
Positive symptoms (follow-up)			
Jones et al, 2012[49]	7 studies / 380 participants	MD −0.90, 95% CI −1.74 to −0.06, *P* = .037 Heterogeneity: I^2 = 7%	NR
Auditory hallucinations (end of treatment)			
van der Gaag et al, 2014[55]	4 studies / 387 participants	SMD 0.49, 95% CI NR, *P* < .05 (favours CBT) Heterogeneity: I^2 = 40.9%	Mean CTAM score = 82 (range 67–93)
Kennedy et al, 2017[50]	2 studies / 105 participants	MD −0.86, 95% CI −2.38 to 0.65, *P* = .26 Heterogeneity: I^2 = 0%	GRADE: moderate
Jones et al, 2012[49]	4 studies / 258 participants	MD −0.92, 95% CI −3.33 to 1.49, *P* = .46 Heterogeneity: I^2 = 0%	NR
Auditory hallucinations (follow-up)			
Jones et al, 2012[49]	6 studies / 267 participants	MD −1.30, 95% CI −4.01 to 1.41, *P* = .35 Heterogeneity: I^2 = 23%	NR
Delusions (end of treatment)			
van der Gaag et al, 2014[55]	5 studies / 411 participants	SMD 0.33, 95% CI NR, *P* = NS (favours CBT) Heterogeneity: I^2 = 62%	Mean CTAM score = 75 (range 49–93)
Jones et al, 2012[49]	4 studies / 311 participants	MD −1.62, 95% CI −3.16 to −0.07, *P* = .041 Heterogeneity: I^2 = 78%	NR
Delusions (follow-up)			
Jones et al, 2012[49]	6 studies / 329 participants	MD −0.89, 95% CI −2.34 to 0.55, *P* = .23 Heterogeneity: I^2 = 0%	NR
Negative symptoms (end of treatment)			
Lutgens et al, 2017[51]	5 studies	SMD −0.11, 95% CI −0.26 to 0.04 Heterogeneity: NR	NR
Jauhar et al, 2014[58]	12 studies	SMD −0.08, 95% CI −0.29 to 0.13, *P* = NR Heterogeneity: NR	NR
Turner et al, 2014[54]	15 studies	SMD 0.04, 95% CI −0.09 to 0.16, *P* = NR Heterogeneity: I^2 = 0% *Excluding high risk of bias (14 studies)* SMD 0.02, 95% CI −0.10 to 0.15, *P* = NR Heterogeneity: I^2 = 0.3% *Excluding low risk of bias (11 studies)* SMD 0.0, 95% CI −0.15 to 0.14, *P* = NR Heterogeneity: I^2 = 0% *Excluding any risk of bias (10 studies)* SMD −0.01, 95% CI −0.15 to 0.14, *P* = NR Heterogeneity: I^2 = 0%	Subgroup analysis undertaken based on risk of bias
Jones et al, 2012[49]	6 studies / 328 participants	MD −0.25, 95% CI −1.09 to 0.59, *P* = .56 Heterogeneity: I^2 = 78%	NR
Negative symptoms (follow-up)			
Jones et al, 2012[49]	7 studies / 380 participants	MD −0.43, 95% CI −1.38 to 0.51, *P* = .70 Heterogeneity: I^2 = 0%	NR

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
Social function (end of treatment)			
Jones et al, 2012[49]	1 study / 65 participants	MD 5.40, 95% CI −5.18 to 15.98, *P* = .32 Heterogeneity: NA	NR
Social function (follow-up)			
Jones et al, 2012[49]	1 study / 65 participants	MD 8.80, 95% CI −4.07 to 21.67, *P* = .18 Heterogeneity: NA	GRADE: very low
Relapse (end of treatment)			
Jones et al, 2012[49]	1 study / 71 participants	RR 0.65, 95% CI 0.21 to 1.95, *P* = .44 Heterogeneity: NA	NR
Relapse (follow-up)			
Jones et al, 2012[49]	5 studies / 350 participants	RR 0.91, 95% CI 0.63 to 1.32, *P* = .63 Heterogeneity: I^2 = 63%	GRADE: low
Quality of life (long term)			
Jones et al, 2012[49]	1 study / 37 participants	MD −1.86, 95% CI −19.20 to 15.48, *P* = .83 Heterogeneity: NA	GRADE: very low
Rehospitalization (short term)			
Jones et al, 2012[49]	2 studies / 136 participants	RR 0.36, 95% CI 0.11 to 1.13, *P* = .079 Heterogeneity: I^2 = 0%	NR
Rehospitalization (long term)			
Jones et al, 2012[49]	5 studies / 294 participants	RR 0.86, 95% CI 0.61 to 1.20, *P* = .37 Heterogeneity: I^2 = 0%	GRADE: low
Adverse events			
Jones et al, 2012[49]	1 study / 198 participants	RR 2.0, 95% CI 0.71 to 5.64, *P* = .19 Heterogeneity: NR	GRADE: very low
Death			
Jones et al, 2012[49]	2 studies / 202 participants	RR 0.57, 95% CI 0.12 to 2.60, *P* = .47 Heterogeneity: I^2 = 0%	NR

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; CTAM, Clinical Trials Assessment Measure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NA, not applicable; NR, not reported; NS, not significant; RR, relative risk; SMD, standardized mean difference.

Cognitive Behavioural Therapy for Psychosis Compared With Any Control

Five systematic reviews compared CBT for psychosis with any control, which may have included usual care and another form of psychotherapy.[51,55-58] Table 3 provides full results for this comparison.

Overall Psychotic Symptoms

One systematic review reported a significant difference in overall psychotic symptoms at the end of treatment, favouring CBT compared with any control.[58] Overall symptoms were calculated based on total scores on general psychiatric scales that rated positive and negative symptoms and other symptoms. Scales used were PANSS, BPRS, CPRS, and the Hopkins Psychiatric Rating Scale.

Positive Symptoms

Two systematic reviews reported a significant difference in positive symptoms at the end of treatment, favouring CBT compared with any control.[57,58] The scales used in studies reviewed

by Jauhar et al[58] included positive symptom subscales of the PANSS, BPRS, the Krawiecka (Manchester) scale, SAPS, and PSYRATS. Wykes et al[57] stated that, in most cases, the primary studies used a summary score from a reliable measure such as PANSS or BPRS.

Auditory Hallucinations

Two systematic reviews reported a significant difference in auditory hallucinations at the end of treatment, favouring CBT compared with any control.[55,58] Scales used in the review by van der Gaag et al[55] included PSYRATS, MMDAS, PDI, CPRS, and BAVQ-R. Jauhar et al[58] stated that most primary studies in their systematic review used the hallucinations scale from PSYRATS.

Delusions

One systematic review reported a significant difference in delusions at the end of treatment, favouring CBT compared with any control.[55] Scales used by studies in the meta-analysis by van der Gaag et al[55] included PSYRATS, MMDAS, PDI, CPRS, and BAVQ-R.

Negative Symptoms

Three systematic reviews reported a significant difference in negative symptoms at the end of treatment favouring CBT compared with any control.[51,57,58] Lutgens et al[51] stated negative symptom outcomes were based on a valid and reliable negative symptom measurement, such as SANS and PANSS. Jauhar et al[58] reported the negative symptom subscale of the PANSS, the SANS, the BPRS negative factor, and a negative symptoms scale derived from the CPRS and from the Krawiecka (Manchester) scale. Wykes et al[57] stated that the primary studies in their review used the PANSS negative symptom score.

One systematic review reported no significant difference in negative symptoms at the end of treatment and at the end of short-term follow-up (3 to 6 months) or long-term follow-up (9 to 12 months) for people who received CBT compared with any control.[56] Velthorst et al[56] stated that the primary studies in their systematic review used the PANSS.

Social Function

One systematic review reported a significant difference in social function at the end of treatment favouring CBT compared with any control.[57] The scale reported by Wykes et al[57] was the Global Assessment of Functioning.

Table 3: Summary of Results, CBT for Psychosis Compared With Any Control

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
Overall psychotic symptoms (end of treatment)			
Jauhar et al, 2014[58]	34 studies	SMD −0.33, 95% CI −0.47 to −0.19, *P* < .001 Heterogeneity: I^2 = 68% *Comparison between studies at high and low risk of bias from masking:* Effect size in 10 unmasked studies was statistically significantly higher than the effect size in 20 masked studies (SMD −0.62, 95% CI −0.88 to −0.35 vs. SMD −0.15, 95% CI −0.27 to −0.03; *P* = .001)	Findings were presented with respect to sequence generation, allocation concealment, masking, and incomplete outcome data
Positive symptoms (end of treatment)			
Jauhar et al, 2014[58]	33 studies	SMD −0.25, 95% CI −0.37 to −0.13, *P* < .001 Heterogeneity: I^2 = 49% *Comparison between studies at high and low risk of bias from masking:* Effect size in 8 unmasked studies was statistically significantly higher than the effect size in 20 masked studies (SMD −0.57, 95% CI −0.76 to −0.39 vs. SMD −0.08, 95% CI −0.18 to 0.03; *P* < .001)	Findings were presented with respect to sequence generation, allocation concealment, masking, and incomplete outcome data
Wykes et al, 2008[57]	32 studies / 1,918 participants	SMD 0.37, 95% CI 0.23 to 0.52, *P* = NR Heterogeneity: Chi^2 = 61.7, *P* = NR *Comparison between studies with high (score of > 65) and low CTAM scores:* The effect is attenuated when restricted to studies with higher CTAM score: effect size in 12 studies with high CTAM scores was higher than in 20 studies with low CTAM scores (SMD 0.22, 95% CI 0.02 to 0.43 vs. SMD 0.49, 95% CI 0.31 to 0.66)	CTAM scores reported by RCT
Auditory hallucinations (end of treatment)			
Jauhar et al, 2014[58]	15 studies	SMD −0.34, 95% CI −0.61 to −0.06, *P* = .01 Heterogeneity: I^2 = 70% *Comparison between studies at high and low risk of bias from masking:* Effect size in 2 unmasked studies was different from the effect size in 12 masked studies (SMD −0.91, 95% CI −2.67 to 0.85 vs. SMD −0.18, 95% CI −0.37 to 0.01; *P* value NR)	Findings were presented with respect to sequence generation, allocation concealment, masking, and incomplete outcome data
van der Gaag et al, 2014[55]	11 studies	SMD 0.44, 95% CI 0.26–0.61, *P* < .005 (favours CBT) Heterogeneity: I^2 = 49%	Mean CTAM score = 67 (range 34–93)
Delusions (end of treatment)			
van der Gaag et al, 2014[55]	9 studies	SMD 0.36, 95% CI 0.08–0.63, *P* = .011 (favours CBT) Heterogeneity: I^2 = 56%	Mean CTAM score = 72 (range 4–93)
Negative symptoms (end of treatment)			
Lutgens et al, 2017[51]	16 studies	SMD −0.34, 95% CI −0.55 to −0.12 Heterogeneity: I^2 = 74%	Medium to high
Velthorst et al, 2015[56]	30 studies / 2,312 participants	SMD 0.09, 95% CI −0.02 to 0.214, *P* = .13 (favours CBT) Heterogeneity: I^2 = 60% A higher CTAM score was associated with a lower effect size (Q value difference = 11.83, *P* = .0006)	CTAM scores reported by RCT

Author, Year	No. of Studies / No. of Participants	Results	Quality Assessment
Jauhar et al, 2014[58]	34 studies	SMD −0.13, 95% CI −0.25 to −0.01, *P* = .03 Heterogeneity: I^2 = 48% *Comparison between studies at high and low risk of bias from masking:* Effect size in 8 unmasked studies was different from the effect size in 22 masked studies (SMD −0.22, 95% CI −0.51 to 0.08 vs. SMD −0.04, 95% CI −0.14 to 0.06; *P* = .26)	Findings were presented with respect to sequence generation, allocation concealment, masking, and incomplete outcome data
Wykes et al, 2008[57]	23 studies / 1,268 participants	SMD 0.44, 95% CI 0.17 to 0.70, *P* = NR (favours CBT) Heterogeneity: Chi^2 = 118.1, *P* = NR *Comparison between studies with high (score > 65) and low CTAM scores:* The effect is attenuated when restricted to studies with higher CTAM score: effect size in 9 studies with high CTAM scores was higher than in 14 studies with low CTAM scores (SMD 0.21, 95% CI −0.10 to 0.52 vs. SMD 0.61, 95% CI 0.2 to 1.02)	CTAM scores reported by RCT
Negative symptoms (at follow-up)			
Velthorst et al, 2015[56]	*Short term (3–6 months)*		
	13 studies	SMD 0.21, 95% CI −0.05 to 0.46, *P* = .113 (favours CBT) Heterogeneity: NR	CTAM scores reported by RCT
	Long term (9–12 months)		
	10 studies	SMD −0.01, 95% CI −0.02 to 0.18, *P* = .922 Heterogeneity: NR	CTAM scores reported by RCT
Social function (end of treatment)			
Wykes et al, 2008[57]	15 studies / 867 participants	SMD = 0.36, 95% CI 0.15 to 0.60, *P* = NR (favours CBT) Heterogeneity: Chi^2 = 36.7, *P* = NR *Comparison between studies with high (score > 65) and low CTAM scores:* The effect is attenuated when restricted to studies with higher CTAM score: effect size in 5 studies with high CTAM scores was higher than in 10 studies with low CTAM scores (SMD 0.15, 95% CI −0.17 to 0.47 vs. SMD 0.51, 95% CI 0.22 to 0.80)	CTAM scores reported by RCT

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; CTAM, Clinical Trials Assessment Measure; NA, not applicable; NR, not reported; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference.

Cognitive Behavioural Therapy for Psychosis in Individuals With First-Episode Psychosis

We identified two systematic reviews that reported on the effects of CBT for psychosis in individuals with first-episode psychosis.[46,52]

Alvarez-Jimenez et al[46] identified three RCTs with a total of 283 participants with first-episode psychosis; these trials investigated the effectiveness of individual CBT for psychosis compared with other forms of therapy. When CBT for psychosis was delivered in combination with a specialist early-intervention program, there was no statistically significant difference in relapse compared with the program alone (pooled odds ratio [OR] 1.95, 95% CI 0.76–5.00, *P* = .17).[46] No difference in relapse was reported when CBT for psychosis was compared with supportive counselling (OR 1.11, 95% CI 0.63–1.95; *P* = .72) or usual care (OR 1.15, 95% CI 0.65–2.04, *P* = .62).[46] The review authors concluded that the available evidence indicated that CBT for

psychosis, in combination with early intervention programs, was not more effective for the prevention of relapse in people with first-episode psychosis than early intervention programs alone.[46]

Marshall and Rathbone[52] looked at CBT for psychosis compared with usual care in individuals who had experienced their first-episode of psychosis. They identified one RCT of 62 people who received CBT for psychosis in 20 sessions of 45 minutes, plus antipsychotic drugs.[52] The control group were given a befriending service in addition to antipsychotic drugs. No significant difference in study attrition (relative risk [RR] 0.57, 95% CI 0.19–1.76) or in the number of people hospitalized over 12 months (RR 1.08, 95% CI 0.59–1.99) was observed between treatment groups.[52] Two people died due to suicide in the CBT group and none in the control group, although this difference was not statistically significant. No statistically significant differences in social functioning were observed by assessment at 12 months (mean difference −1.30, 95% CI −8.86 to 6.26).[52] Similarly, no significant differences in positive symptoms (mean difference 0.35, 95% CI −1.86 to 2.56) and negative symptoms (mean difference 4.89, 95% CI −1.58 to 11.36) were observed between the two treatment groups.[52]

Brief or Low-Intensity CBT for Psychosis

We found two systematic reviews that investigated the effectiveness of low-intensity or brief CBT for psychosis.[48,53]

Hazell and colleagues[48] identified nine studies that compared low-intensity CBT for psychosis—defined as fewer than 16 sessions of face-to-face contact time—with any control group. This systematic review reported a statistically significant improvement in overall psychotic symptoms in the intervention group of low-intensity CBT for psychosis compared with control groups, both at the end of treatment and at follow-up (Table 4).[48] No statistically significant difference in effect size for social function was observed at the end of treatment, although at follow-up the difference was significant (Table 4).[48] The mean quality score for the included studies using the Downs and Black scale was 24.80 out of 31 (range 18–29).[48] A moderation analysis to examine the impact of study quality on effect estimates found no impact (Spearman's *rho* = 0.39, *P* = .30).[48]

The second systematic review, by Naeem and colleagues,[53] aimed to compare the effects of brief CBT for people with schizophrenia against standard CBT for psychosis, but no relevant studies were identified.

Table 4: Summary of Results, Low-Intensity CBT for Psychosis

Outcome	No. of Studies / No. of Participants	Results[a]
Overall psychotic symptoms (end of treatment)	9 studies / 631 participants	SMD −0.46, 95% CI −0.86 to −0.06; *P* = .03 Heterogeneity: *Q* = 34.0, *P* < .001
Overall psychotic symptoms (follow-up)	6 studies / 494 participants	SMD −0.40, 95% CI −0.74 to −0.06, *P* = .02 Heterogeneity: *Q* = 13.79, *P* = NR
Social function (end of treatment)	4 studies	SMD −0.39, 95% CI −0.82 to 0.40, *P* = .07 Heterogeneity: *Q* = 0.16, *P* < .05
Social function (follow-up)	4 studies	SMD −0.57, 95% CI −0.81 to −0.33, *P* < .001 Heterogeneity: *Q* = 1.80, *P* = NR

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; NR, not reported; SMD, standardized mean difference.
[a]Studies included in this systematic review compared brief or low-intensity CBT with any control.
Source: Hazell et al, 2016.[48]

Group CBT for Psychosis Compared With Individual CBT for Psychosis

We did not identify any systematic review with the specific aim of comparing the effectiveness of group and individual CBT for psychosis. However, two systematic reviews undertook this comparison in subgroup analyses.[54,57]

Turner and colleagues[54] investigated the potential differential effects of group or individual format CBT for psychosis by entering intervention format as a moderator variable (Table 5). The between-group comparisons for group versus individual CBT for psychosis were not statistically significant; however, the comparison was limited by low power.[54]

In the subgroup analysis by Wykes and colleagues,[57] the estimated effect size for overall symptoms for the 26 studies of individual CBT for psychosis was 0.415 (standard error 0.08), compared with 0.386 (standard error 0.20) for seven studies of group CBT (95% CI 0.384–0.442). This demonstrated no statistically significant difference in the effect on target symptoms between individual and group CBT for psychosis.

Table 5: Summary of Subgroup Analysis Comparing Individual With Group CBT for Psychosis

Outcome	Individual CBT for Psychosis	Group CBT for Psychosis	Statistical Significance of Difference
All symptoms	SMD 0.18, 95% CI 0.05 to 0.32	SMD 0.00, 95% CI −0.26 to 0.27	*P* = .24
Positive symptoms	SMD 0.16, 95% CI 0.02 to 0.30	SMD 0.12, 95% CI −0.13 to 0.36	*P* = .80
Negative symptoms	SMD 0.09, 95% CI −0.06 to 0.23	SMD −0.11, 95% CI −0.35 to 0.14	*P* = .19

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; SMD, standardized mean difference.
Source: Turner et al, 2014.[54]

Physician Service Providers Compared With Nonphysicians

We identified no systematic review that compared the effectiveness of physician and nonphysician service providers for the delivery of CBT for psychosis.

Online/Internet CBT for Psychosis Compared With In-Person CBT for Psychosis

We found no systematic reviews comparing Internet-based delivery of CBT for psychosis with in-person therapy.

Discussion

In summary, the evidence from systematic reviews shows that CBT for psychosis significantly improved overall psychotic symptoms, positive symptoms, auditory hallucinations, delusions, and negative symptoms, compared with usual care or any control at the end of treatment.[47,49,54,55,57,58] At follow-up, however, the available research has not shown an improvement in positive or negative symptoms for people who received CBT for psychosis compared with those receiving usual care,[47] and has not shown an improvement in negative symptoms compared with any control.[56] (Follow-up was not well reported across the systematic reviews but was generally 9 to 12 months.) Compared with other forms of psychotherapy, CBT for psychosis showed inconsistent results at end of treatment for overall psychotic symptoms, positive symptoms, auditory hallucinations, and delusions.[49,50,54,55,58] Brief or low-intensity CBT compared with any control showed significant improvement for overall psychotic symptoms at end of treatment and social function at follow-up in one systematic review,[48] but another review hoping to compare the effects of brief and standard CBT for psychosis was unable to identify any studies that specifically compared the two types of therapy for treatment of psychosis.[53]

The limitations of our review include that (1) it is an overview of systematic reviews and therefore may have missed recently published trials, and (2) different methods were used by authors of the included systematic reviews for evaluating the quality of evidence.

The systematic review authors who used GRADE to evaluate the evidence generally reported the overall quality of the studies as low to moderate; authors who used other tools generally reported the evidence quality as adequate; and some studies were not assessed.

For studies focusing on treatment of first-episode psychosis, the authors of the systematic reviews generally reported a low or unclear risk of bias within the included studies. As treatment for first-episode psychosis, CBT for psychosis did not significantly improve any outcomes compared with other forms of psychotherapy or usual care. One possible explanation is that usual treatment for a first-episode of psychosis may be more comprehensive than in later stages of the illness.

The definition of usual care in the studies reviewed typically included antipsychotic medication but there was some variability.[49] For example, in the systematic review by Jones et al,[49] one study was limited to participants treated with olanzapine for at least 6 months, whereas another study intentionally selected people with medication-resistant symptoms.

Some CBT for psychosis interventions varied with regard to both the target of the therapy and the specificity of focus.[49] For example, one study included in the systematic review by Jones et al[49] used a CBT for psychosis intervention focused specifically on medication compliance, while the CBT for psychosis intervention described by another author had a wider focus, incorporating not only medication compliance but also auditory hallucinations and delusions, anxiety, depression, and relapse prevention. Overall, studies used variable criteria for relapse.[49]

The period of active therapy also varied among many trials.[49] For example, one study included in the systematic review by Jones et al[49] provided up to 8 weeks of individual CBT for psychosis while another study gave up to 9 months of both individual and group CBT for psychosis over the course of recovery, as well as family engagement aimed at developing familial coping strategies and a structured activity program (for an average of 5 hours per week) including cooking, creative therapy, and discussion groups.

Our assessment was limited to some degree because of the lack of clear, explicit definitions of both brief and standard CBT for psychosis and of therapists' training and expertise.[53] In particular, the duration of therapists' experience with delivering CBT for psychosis is not always clearly described in the trials; therefore, it is difficult to conduct sensitivity analyses to determine the effect of therapist expertise.[49]

To compare individual and group CBT for psychosis, two systematic reviews reported subgroup analyses,[54,57] but neither explicitly stated whether these analyses were decided a priori. Overall, individual and group CBT for psychosis showed no significant difference in target symptoms.

Few systematic reviews reported on adverse effects, patient satisfaction, quality of life, or patient engagement with services.[49]

Ongoing Studies

Three systematic reviews with potential relevance to this overview of reviews were identified through a search of the international prospective register of systematic reviews (PROSPERO) (Appendix 5).[59-61] We also found two potentially relevant published Cochrane protocols when searching the Cochrane Database of Systematic Reviews (Appendix 5),[62,63] but we did not find published reviews in the Cochrane Database.

Conclusions

Compared with usual care or any control, cognitive behavioural therapy (CBT) for psychosis significantly improved overall psychotic symptoms, positive symptoms, auditory hallucinations, delusions, and negative symptoms. The overall quality of the studies was generally reported as moderate or adequate, or it was not assessed by the systematic review authors.

Compared with other forms of psychotherapy, CBT for psychosis showed inconsistent results regarding improvement in overall psychotic symptoms, positive symptoms, auditory hallucinations, and delusions. The systematic review authors generally reported the overall quality of studies as moderate.

In people with first-episode psychosis, CBT for psychosis did not significantly improve any outcomes compared with other forms of psychotherapy or usual care (low or unclear risk of bias reported by the systematic review authors).

One systematic review found that brief or low-intensity CBT for psychosis showed significant improvement compared with any control for overall psychotic symptoms and social function at follow-up, based on a quality of evidence reported as moderate or adequate by the systematic review authors.

Subgroup analyses from two systematic reviews comparing individual and group CBT for psychosis showed no significant difference in target symptoms between individual and group CBT for psychosis.

We found no systematic reviews that compared physician service providers with nonphysicians for the delivery of CBT for psychosis, or that compared online/Internet CBT for psychosis with in-person CBT for psychosis.

We also found no systematic reviews of adverse effects related to CBT for psychosis. The systematic reviews reported sparsely, if at all, on the safety of this therapy.

ECONOMIC EVIDENCE

Research Question

What is the incremental cost-effectiveness of cognitive behavioural therapy (CBT) for psychosis over usual care in the management of adults with schizophrenia?

Methods

Economic Literature Search

We performed economic literature searches on April 5, 2017, for studies published from inception to the search date. Methodological filters were applied to the clinical search to limit retrieval to economic evaluations, cost, quality of life, and health utilities studies.[64,65]

We created database auto-alerts in MEDLINE, Embase, PsycINFO, and CINAHL and monitored them for the duration of the health technology assessment. We performed targeted grey literature searching of health technology assessment agency websites, clinical trial registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Evidence Review, Literature Search, above, for further details on methods used and Appendix 1 for literature search strategies, including all search terms.

Literature Screening

A single reviewer screened titles and abstracts using DistillerSR management software. Full-text articles of the potentially eligible studies were reviewed, and reasons for exclusion were recorded for studies that did not meet the eligibility criteria. Reference lists of included studies were screened for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language individual-level (patient-level) or decision-modeling economic evaluations that met the following criteria:
    - Compared usual care to CBT for psychosis in management of adults with schizophrenia
    - Reported an incremental cost-effectiveness ratio (ICER) or an incremental net benefit (INB)

Exclusion Criteria

- Systematic or narrative reviews, study protocols, guidelines, conference abstracts, commentaries, letters, and editorials
- Comparative studies comparing only the costs of interventions, non-comparative studies reporting costs of CBT for psychosis, or cost of illness studies
- Cost-effectiveness studies related to application of CBT for psychosis in the prevention of first-episode psychosis in people with prodromal symptoms but not confirmed schizophrenia

Types of Participants

Population of interest was adults (aged 18 years and older) with schizophrenia: first-episode, recurrent, or treatment-resistant.

Types of Interventions

The intervention of interest was CBT for psychosis, alone or combined with pharmacotherapy, provided in-person by various health care providers (e.g., psychiatrists, clinical psychologists) as group or individual therapy.

The comparator was usual care, which consisted of pharmacotherapy but could also include psychoeducation or counselling services, family therapy, or social and vocational services.[8-10,19,28]

Outcomes of Interest

We examined the following outcomes: incremental costs, incremental effectiveness (e.g., incremental quality-adjusted life-years [QALYs]), and ICER or INB.

Data Extraction

We extracted relevant data on the following:

- Source (i.e., first author, location, year)
- Population
- Interventions and comparators
- Outcomes (i.e., health outcomes, costs, and cost-effectiveness)

Study Applicability and Limitations

A single reviewer determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations that was originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform development of NICE's clinical guidelines.[66] We modified the wording of the questions to remove references to guidelines and to make it Ontario-specific. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of the study to the research questions (directly, partially, or not applicable). A summary is presented in Appendix 6. In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly or partially applicable.

Results

Literature Search

The database and grey literature searches yielded 551 citations published from inception to April 5, 2017 (with duplicates removed). We excluded a total of 534 articles based on information in the title and abstract and obtained 17 full-text articles for further assessment. Six studies met the inclusion criteria and were assessed to establish the applicability of their findings to the Ontario context. Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the economic evidence review.[45]

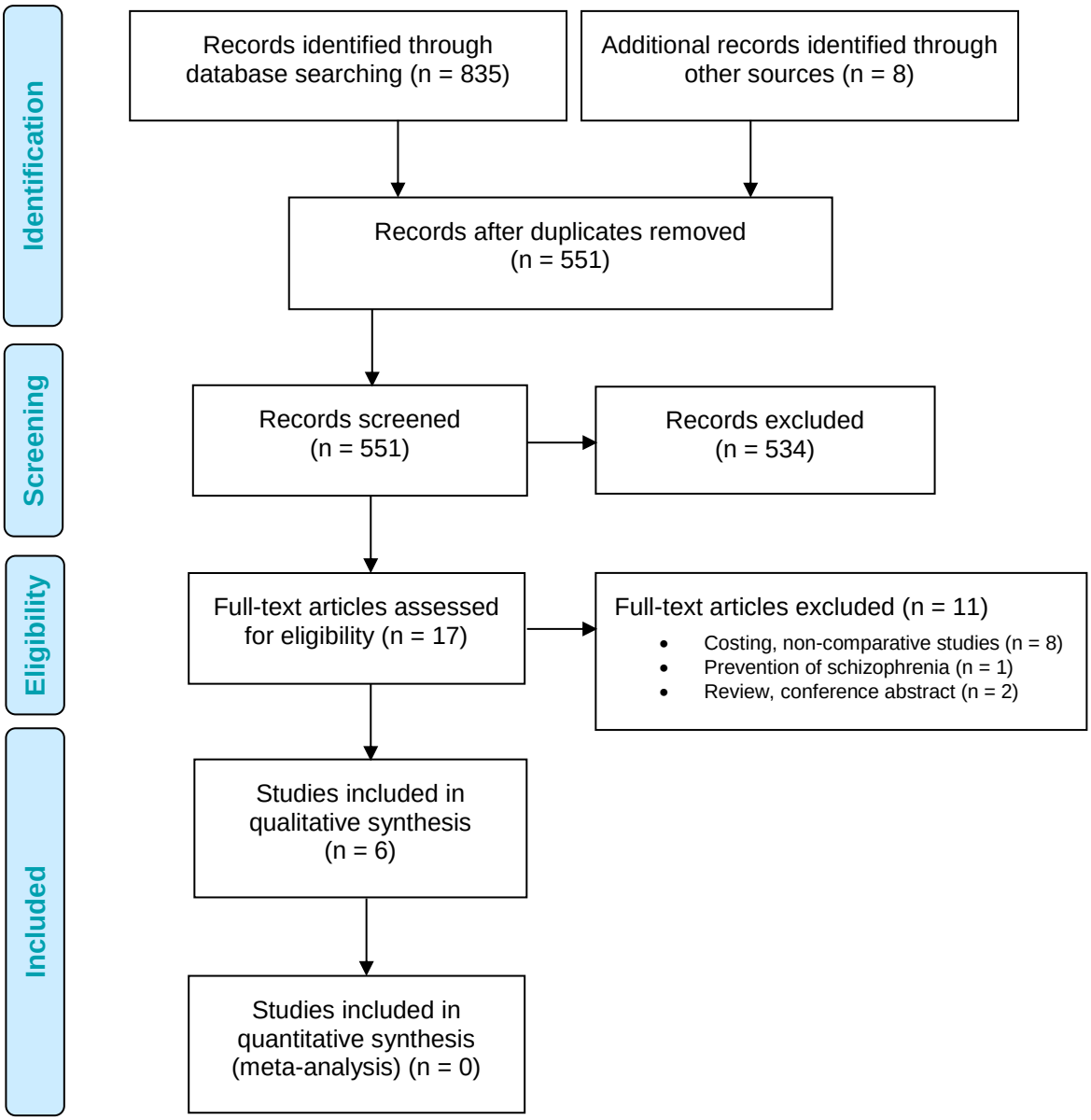

Figure 2: PRISMA Flow Diagram – Economic Search Strategy

Source: Adapted from Moher et al, 2009.[45]

Review of Included Economic Studies

All 6 eligible studies were cost-effectiveness analyses conducted alongside randomized controlled trials (RCTs).[23-26,29,30] Additional results of one economic analysis by Stant et al[26] were published separately[67] and were considered in our review. To prevent duplication, we counted these two publications as one study. Characteristics and results of the included studies are summarized below and in Table 6.

Study Design

Five patient-level economic evaluations were done alongside open-label single or multicentre RCTs,[23,25,26,29,30] and one was conducted alongside a single-blind RCT[24] where the assessors were blinded to treatment allocation. Trial duration and study time horizon ranged from 9 to 18 months.

Five studies were conducted in Europe (the Netherlands[26,29] and United Kingdom[23-25]) and one in China.[30] Four studies took a societal perspective accounting for direct and indirect medical costs and direct nonmedical costs,[24,26,29,30] while two UK studies adopted the health care payer perspective, accounting for health care and social services costs.[23,25]

Study Population

The onset of schizophrenia and duration of treatment widely ranged among the included studies. Four economic analyses included adults (mean age, 26–38 years; 50%–72% males), with a mix of chronic or treatment-resistant schizophrenia disorders who, on average, were treated for 2 to 8 years.[24,26,29,30] One study included adults with affective and nonaffective disorders (i.e., schizophrenia, schizoaffective disorders, bipolar depression, and psychotic schizophrenia) and no stable employment who, on average, were treated 5 years.[23] One study included adults with first-episode psychosis (mean age, 26 years; males, 50%–74%).[25]

Most of the studies excluded people with schizophrenia and drug or alcohol addiction, those with severe learning disability, and those with brain damage. Only one study indicated a lack of competence in the native language as an exclusion criterion.[29]

The sample size varied in the examined studies, ranging from 36 to 1,184; the largest sample was in a Chinese study of adults with stable schizophrenic disorders.[30]

Intervention

In all the economic studies, CBT for psychosis was combined with medications. It was often accompanied with case management[23,25,26,29,30] as a necessary part of clinical practice in the management of this disease.[8-10,19,28] The intervention was provided as the only therapy in one study[29] and, in other studies, was embedded within more complex interventions including family therapy, vocational intervention, coping and motivational training, and psychoeducation.[23-26,30] No study examined the cost-effectiveness of Internet-based (computerized) CBT for psychosis in adults with schizophrenia.

The duration of in-person individual or group CBT for psychosis was 45 to 60 minutes, with therapy provided weekly in all but one study[30] and lasting, on average, 9 months (range, 9 to 18 months). In an RCT by van der Gaag et al,[29] individual CBT for psychosis was delivered in two steps: (1) pre-therapy of maximally 4 weekly sessions provided by a CBT assistant or a trained nurse, and (2) CBT therapy of maximally 26 weekly sessions delivered in a structured 6-step

approach (Table 6). Zhang et al[30] conducted the largest study and, within their 12-month psychosocial service program, they organized group CBT for psychosis for groups of 6 participants. This group therapy was delivered in monthly, 60-minute sessions.

Most of the studies reported on training requirements for the health professionals who provided CBT for psychosis.[23-25,29,30] The therapy was provided by nonphysician therapists and case managers specifically trained and certified in CBT for psychosis,[23,24] and by medical doctors with at least 2 years of clinical experience or PhDs in clinical psychology with over 5 years of clinical experience.[30] In a study by McCrone et al,[25] which included people with first-episode psychosis, the providers were part of an early-psychosis team of 10 staff members consisting of various health care professionals (psychiatrists, psychologists, occupational therapists, nurses and health care assistants specifically trained to provide care to people with early psychosis).

Comparator

All RCTs used usual care as a comparator. Usual care typically consisted of multiple interventions including medications, psychosocial counselling, community services, and case management.

Measurement of Study Outcomes and Results

Clinical effectiveness of CBT for psychosis was measured by four health outcomes: (1) the mean change from baseline as determined by several clinical questionnaires assessing symptoms and global functioning such as the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning Scale (GAF) or Manchester Short Assessment of Quality of Life (MANSA)[24-26]; (2) the mean difference in a percentage of relapsed patients[30]; (3) the number of days with normal functioning, measured by the Social Functioning Scale (SFS) and the Psychotic Symptom Rating Scales (PSYRATS)[29]; (4) the mean difference in QALYs, where utility values were mapped from the EQ-5D or SF-6D, two questionnaires that capture health-related quality of life.[23,26,30,67]

As shown in Table 6, all economic analyses alongside RCTs found statistically significant improvements in health outcomes after 9 to 12 months of CBT for psychosis. Stant et al[26,67] showed that the increment in QALYs (CBT for psychosis vs. usual care) achieved at 9 months was maintained at 18 months of follow-up. Similarly, Barton et al[23] and Zhang et al[30] showed increments in QALYs of 0.035 and 0.031 after 9 and 12 months of CBT for psychosis, respectively.

Depending on the study perspective, total costs included direct medical and social services costs (i.e., health care payer perspective[23,25]) or they included all types of costs such as direct medical costs, direct nonmedical costs, and indirect (productivity loss) costs (i.e., societal perspective[24,26,29,30]). Two studies[23,25] collected direct medical costs, social services use, and contacts with the criminal justice system (i.e., police cell costs and prison costs) using a validated resource-use questionnaire (i.e., the Client Service Receipt Inventory[68]). Intervention costs were part of direct medical costs; the costs of providing the CBT for psychosis included therapist time (salary, number of sessions), supervision time, and other clinically applicable time. Other components of direct medical costs included inpatient care, sheltered accommodation and day care, outpatient and community care, general health services (general practitioner/psychiatrist visits), and medications. Studies that used a societal perspective estimated the costs of travel and parking and the time invested in therapy as direct nonmedical costs related to the intervention. Direct nonmedical costs also included informal care, costs of

travel for the purpose of medical visits, and out-of-pocket costs, as well as costs associated with productivity loss.

As shown in Table 6, three economic analyses found usual care more costly compared with CBT for psychosis,[24-26] and another three analyses found CBT for psychosis more costly than usual care.[23,29,30]

Cost-Effectiveness Results

In cost-effectiveness analyses, the ICER was expressed as the incremental cost per clinically relevant effectiveness outcome: for example, the cost per one recurrence (relapse) avoided, cost per symptom-free day, cost per point change in a symptom-scale score, or cost per life-year saved. In cost-utility analyses, the ICER was expressed as the cost per one QALY gained.

All economic evaluations had favourable findings regarding the cost-effectiveness of CBT for psychosis over usual care. The three cost-effectiveness analyses[24-26] that examined point improvement in symptoms or functional status, as measured by valid and reliable questionnaires (e.g., PANSS), showed that CBT for psychosis was dominant. That is, CBT for psychosis was either cost saving (it was less expensive than usual care and associated with improvement in functional status) or cost-effective. The probability of CBT for psychosis being cost-effective ranged from 69%[24] to 92%[25] even when the studies assumed that a decision-maker or a society would not be willing to pay any amount of money for a one-point improvement in functional status. A cost-effectiveness analysis by van Gaag et al[29] in adults with treatment-resistant schizophrenia, which measured the number of days during which participants functioned within the normal range, showed an ICER of €47 per additional day with normal functioning for CBT for psychosis versus usual care. The probability of CBT for psychosis being cost-effective ranged from 21% at a willingness-to-pay threshold of €0 per additional day with normal functioning to 90% at a willingness-to-pay threshold of €250 per additional day of normal functioning.[29] In economic analyses by Barton et al[23] and Zhang et al,[30] CBT for psychosis represented good value for money at the willingness-to-pay thresholds of £20,000 and $US5,100 per one QALY gained, respectively, with ICERs of £18,844 per QALY and $US1,819 per QALY. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability of CBT for psychosis being cost-effective was 54%.[23]

Table 6: Results of Economic Literature Review—Summary, Cost-Effectiveness of CBT for Psychosis in Treatment of Schizophrenia

Name, Year, Location	Methods			Results		
	Study Design and Perspective	Population / Study Outcomes	Interventions / Comparators	Health Outcomes	Costs	Cost-Effectiveness
Stant, 2003, Netherlands [26,67]	• Individual-level cost-effectiveness analysis • Open-label RCT • Netherlands, societal perspective • Time horizon: 18 months • Discount rate: 4%	• Adults with chronic schizophrenia, schizoaffective disorder, or psychosis + persistent auditory hallucinations (DSM-IV) for 2 y (mean duration: 10–13 y), treated with > 2 antipsychotics; excluded: prior CBTp, drug or alcohol abuse, IQ > 80 • Total N: 63[a] • Mean age, intervention vs. control, y: 36.3 (SD 11.1) vs. 35.3 (SD 10.6) • Males, intervention vs. control: 55% vs. 53% • Outcomes: 1) mean change from baseline in the PANSS score; 2) QALYs; 3) total costs • Total costs: 1) HIT intervention costs; 2) direct medical costs; 3) direct nonmedical costs; 4) indirect nonmedical costs	• Intervention (n = 32): HIT consisting of CBTp, medications, psych-education, coping and motivational training, rehabilitation, and single family treatment • Control (n = 31): usual care, medications, home visits, psychoeducation, and supportive counselling • HIT provided over 9 mo, with approximately 11 contacts with HIT team • Duration and frequency of CBT sessions: NR	• Mean PANSS score, intervention vs. usual care: Baseline: 57.1 vs. 60.2; 9 mo: 51.0 vs. 61.7; 18 mo: 51.1 vs. 57.3 • Change from baseline in PANSS scores, intervention vs. usual care: 9 mo: 6.1 vs. 1.5, *P* < .01 (95% CI: NR) 18 mo: 6.0 vs. 2.9 (*P* = .40, 95% CI −4.23, 10.55) • Mean QALYs at 18 mo, intervention vs. usual care: 1.0 (0.3) vs. 1.0 (0.3) • Mean difference in QALYs, intervention vs. usual care: 0 (*P* = .98, 95% CI −0.15, 0.14)	• Currency, year: US$, 2000 • Total costs (mean), CBTp vs. usual care: $18,237 vs. $21,436 (*P* > .05) • Mean difference, CBTp vs. usual care: −$3,413 (95% CI −$12,050 to $6,637)	• Base-case analysis, intervention vs. usual care: cost-saving; −$936 per 1-point improvement in the PANSS score • Probability of cost-effectiveness of HIT was 79% at a willingness-to-pay threshold of $2,000 per point improvement and never exceeded 85% for any willingness-to-pay threshold • Probability of cost-effectiveness of HIT was ~75% at any willingness-to-pay threshold expressed in $/QALY
Haddock, 2003, UK[24]	• Individual-level cost-effectiveness analysis • Single-blinded RCT • UK, societal perspective • Time horizon: 18 months	• People with chronic schizophrenia, schizoaffective disorder or delusional disorder (DSM-IV); excluded: people with organic brain disease or learning disability	• Intervention (n = 18): CBTp plus motivational intervention plus family intervention, in addition to medications • Control (n = 18): usual care, medications, and family support service	• Mean GAF score, CBTp vs. usual care: 49.67 (SD 11.96) vs. 53.33 (SD 13.53) at baseline, 60.12 (SD 18.96) vs. 53.44 (SD 13.00) at 18 mo • Mean difference, GAF score, CBTp vs. usual	• Currency, year: £, 1998/99 • Total costs (mean), CBTp vs. usual care: £8,753 (SD 4,804) vs. £10,013 (SD 10,717) • Mean difference, CBTp vs. usual care: −£1,260	• Base-case analysis, CBTp vs. control: cost-saving • Probability of CBTp being cost-effective ranges from 69% for a willingness-to-pay threshold of £0 per point improvement, to

Name, Year, Location	Methods			Results		
	Study Design and Perspective	Population / Study Outcomes	Interventions / Comparators	Health Outcomes	Costs	Cost-Effectiveness
	• Discount rate: 6%	• Total N: 36, patient/carer dyads • Mean age, patients: NR • Males, patients: NR • Outcomes: 1) mean change from baseline in GAF score; 2) mean change from baseline in PANSS score; 3) number of relapses; 4) total costs • Total costs: 1) intervention costs (CBTp + family intervention sessions, costs of administration and supervision); 2) costs of family support services for patients and caregivers; 3) direct medical costs 4) direct nonmedical costs; 5) indirect costs	• 9-month intervention: individual CBTp plus motivational intervention provided in 29 sessions; family intervention, 10–16 sessions; minimum dose, 10 sessions of both interventions • CBTp provided by therapists, specifically trained and certified	care: −6.68 vs. −0.11 (P = .048) • Relapses at 18 mo, CBTp vs. usual care: 7 vs. 12	(95% CI −£6,978 to £4,459)	70% for a willingness-to-pay threshold of £20 per point improvement, to 90% for a willingness-to-pay threshold of £655 per point improvement
Barton, 2009, UK[23]	• Individual-level cost-utility analysis • Open-label RCT • UK, NHS and PPS perspective • Time horizon: 9 months • Discount rate: 0%	• People with affective or non-affective psychosis including schizophrenia, schizoaffective disorder, bipolar disorder, and psychotic depression, and illness duration ≤ 8 y (mean, 4.8 y), positive psychotic symptoms (PANSS score ≤ 4) and currently unemployed or employed < 16 hr/wk. Excluded: acute psychosis, organic brain disease, or drug/alcohol addiction	• Intervention (n = 35): CBTp plus vocational intervention plus case management • Control (n = 42): Usual care, case management • 9-month intervention: individual social-recovery oriented CBTp, on average 11 sessions, lasting 55 min • CBTp provided by therapists or case	• Mean QALY, CBTp vs. control: 0.041 vs. 0.006 • Mean difference, CBTp vs. control: 0.035	• Currency, year: £, 2006/07 • Total costs (mean), usual care vs. CBTp: £92.21 vs. £576.26 • Mean difference, usual care vs. CBTp: £668.47	• Base-case analysis, CBT vs. control, ICER: £18,844/QALY • Probability of CBTp being cost-effective was 54.3% for a willingness-to-pay threshold of £20,000/QALY • EVPI: £3,365/patient

Name, Year, Location	Methods			Results		
	Study Design and Perspective	Population / Study Outcomes	Interventions / Comparators	Health Outcomes	Costs	Cost-Effectiveness
		• Total N: 77 • Mean age: 28.9 y (range 18–52 y) • Males: 71.4% • Outcomes: 1) QALYs; 2) total costs • Total costs: 1) CBTp costs; 2) direct medical costs	managers, specifically trained and certified			
McCrone, 2010, UK[25]	• Individual-level cost-effectiveness analysis • Open-label RCT, block randomization • UK, NHS and PPS perspective • Time horizon: 18 months • Discount rate: 0%	• People with the first episode of psychosis; excluded: organic psychosis or drug/alcohol addiction • Total N: 144 • Mean age, CBTp vs. control: 26 (SD 6) vs. 27 (SD 6) y • Males, CBTp vs. control: 55% vs. 74% • Outcomes: quality of life measured by MANSA; vocational recovery (% returning to or starting full-time employment); total costs • Total costs: intervention including CBTp costs; direct medical costs; social care services costs	• Intervention (n = 71): structured early psychosis intervention including CBTp, low-dose medications, family therapy and vocational rehabilitation with assertive follow-up by a multidisciplinary team • Comparator (n = 73): usual care including medications and community health services, follow-up provided by a generic mental health team with no extra training in delaying early psychosis • 18-month intervention; method of CBTp delivery NR • Early psychosis team consisted of 10 staff members: psychiatrists, psychologists, occupational therapists,	• Mean MANSA score, CBTp vs. control: 59.3 (SD 12.6) vs. 53.3 (SD 12.4) • Mean difference, CBTp vs. control: unadjusted: 6 (*P* = .025); adjusted: 6 (*P* = .05) • Vocational recovery, CBTp vs. control: 32.8% vs. 21%	• Currency, year: £, 2003/04 • Total costs (mean), CBTp vs. usual care: £11,685 (SD 14,032) vs. £14,062 (SD 18,004) • Mean difference, CBTp vs. usual care: analysis adjusted for baseline costs: −£2,318 (95% CI −£8,128 to £3,326); analysis adjusted for participant characteristics: −£1,756 (95% CI −£4,714 to £8,226)	• Base-case analysis, CBT vs. control, ICER, £ per point change on MANSA: cost-saving • Probability of CBTp being cost-effective was 92% for a willingness-to-pay threshold of £0 per point change on MANSA • Probability of CBTp being cost-effective for achieving vocational recovery was 70% to 80% for a willingness-to-pay threshold of £0

Name, Year, Location	Methods			Results		
	Study Design and Perspective	Population / Study Outcomes	Interventions / Comparators	Health Outcomes	Costs	Cost-Effectiveness
			nurses, health care assistants specifically trained in early psychosis			
van der Gaag, 2011, Netherlands [29]	• Individual-level cost-effectiveness analysis • Open-label RCT, stratified randomization (6 regions) • Netherlands, societal perspective • Time horizon: 18 months • Discount rate: 0%	• People aged 18–64 y, with treatment-resistant schizophrenia or schizoaffective disorder (DSM-IV). Exclusion: severe addiction, no competence in the Dutch language, learning disability, prior exposure to CBTp • Total N: 216 • Mean age, CBTp vs. control: 36.5 (SD 11.2) vs. 37.5 (SD 10.6) y • Males, CBTp vs. control: 69% vs. 73% • Outcomes: 1) number of days functioning within the normal range by SFC and PSYRATS); 2) total costs: • Total costs: 1) CBTp costs (CBT sessions, staff training and supervision, office and accommodation); 2) direct medical costs; 3) direct nonmedical costs; 4) indirect costs	• Intervention: CBTp in addition to medications (n = 109) • Comparator, usual care: medications plus community health care services (n = 97) • Intervention, provided in 2 stages: pre-therapy (max 4 weekly sessions by CBT assistant nurse) and CBT therapy (max 26 weekly sessions) • CBT therapy took structured 6-step approach: pre-therapy training, consumer information and mutual roles, assessment, shared case formulation and goal setting, changing dysfunctional cognitions into more functional thoughts and consolidation • Median number of sessions was 3 by nurse therapists and 13 by psychologists	• Mean number of days with normal functioning, CBTp vs. usual care: 183 vs. 106 • Mean difference, number of days with normal functioning, CBTp vs. usual care: 77 (95% CI: 29.7 to 124.0)	• Currency, year: €, 2007 • Total costs (mean), CBTp vs. usual care: €33,130 vs. €29,578 • Mean difference, CBTp vs. usual care: €3,552 (95% CI: −€5,162 to €12,184)	• Base-case analysis, CBTp vs. control: €47 per day with normal functioning gained • The probability of CBTp being cost-effective ranged from 21% for a willingness-to-pay threshold of €0 per additional day of normal functioning, 70% at a threshold of €84 per additional day of normal functioning and 90% at a threshold of €200–250 per additional day of normal functioning • 3 sensitivity analyses: 1) exclusion of the outlier centre (5% of participants): ICER, €24/additional day; 2) adjustment of the threshold for normal functioning: ICER, €61/additional day; 3) exclusion of patients admitted to a hospital during the 3 months before the study start: ICER, €14/additional day

Name, Year, Location	Methods			Results		
	Study Design and Perspective	Population / Study Outcomes	Interventions / Comparators	Health Outcomes	Costs	Cost-Effectiveness
Zhang, 2014, China[30]	• Individual-level cost-effectiveness analysis • Open-label RCT • China, societal perspective • Time horizon: 12 months • Discount rate: 0%	• People aged 18–50 y with stable schizophrenia or schizoaffective disorder (DSM-IV) diagnosed in the past 5 years treated with one type of oral antipsychotic; excluded: treatment switch or treatment resistance, pregnancy, any other serious, unstable medical condition • Total N: 1,184 • Mean age, CBT vs. control: 26.1 (SD 7.6) vs. 26.3 (SD 8.0) y • Males, CBTp vs. control: 54% vs. 56% • Outcomes: QALYs; % relapse; % hospitalized total costs • Total costs: intervention costs (development, training, services, travel, salary); direct medical costs; nonmedical costs; indirect costs	• Intervention (n = 580): psychosocial intervention consisting of group CBTp, psychoeducation, family intervention and skills training plus medications • Control (n = 604): brief intervention, case management with medication and supportive interventions • Intervention: 4 different interventions, including group CBT (6 people/ group) delivered in 12 1-hour monthly sessions by trained therapists (MD with 2 years of clinical experience and PhD with ≥ 5 years of experience after earning MSc in clinical psychology)	• Mean QALY, intervention vs. control: NR • Mean difference, QALY, intervention vs. control: 0.031 (*P* =.039) • Relapse, intervention vs. control: 14.6% vs. 22.5% (*P* < .001)	• Currency, year: $US, 2005 • Total costs (mean), intervention vs. control: NR • Mean difference, intervention vs. control: $56.4	• Base-case analysis: intervention vs. control, ICER: $1,819/QALY (less than a calculated willingness-to-pay threshold of $5,100/QALY) • Deterministic sensitivity analyses: - reduced number of participants per group (3 instead of 6): ICER, $4,497/QALY - cost of workshop increased by 20%: ICER, $2,206/QALY - clinical effect of therapy decreased by 20%: ICER, $4,339/QALY

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; EVPI, expected value of perfect information; GAF, Global Assessment of Functioning Scale; HIT, Hallucination-focused Integrative Treatment; hr, hour; ICER, incremental cost-effectiveness ratio; MANSA, Manchester Short Assessment of Quality of Life; min, minutes; mo, month; NHS, National Health Service; N, number; NR, not reported; PANSS, Positive and Negative Syndrome Scale; PPS, Partners Procurement Service; PSYRATS, Psychotic Symptom Rating Scales; QALY, quality-adjusted life-years; RCT, randomized controlled trial; SD, standard deviation; SFC, Social Functioning Scale; vs, versus; wk, week; y, year.
[a]Included in cost-effectiveness analysis based on complete case analysis, 83% of the initial sample (N = 76).[26,69]

Applicability and Limitations of the Included Studies

We deemed six studies partially applicable to our research question, as they were similar with respect to our reference case population and comparators (see Appendix 6, Table A5). Although these studies adequately measured costs and resource use, their duration was short, the majority examined short-term or surrogate, clinical outcomes (e.g., changes in positive/negative symptoms), and, therefore, the long-term benefits and cost-effectiveness of CBT for psychosis remain inconclusive. Lastly, none of the studies was conducted in Canada, so their findings could not be directly translated to the context of Ontario's health care system.

We further assessed the limitations of the included studies, as shown in Appendix 6, Table A6. All six studies had a short length of follow-up. In addition, two studies had minor methodological limitations,[23,29] and the other four studies[24-26,30] had three or more limitations such as exclusion of relevant health outcomes, unclear estimation of relative treatment effects or incremental outcomes, and incomprehensive assessment of the parameter uncertainty and its influence on the cost-effectiveness results.

Discussion

We systematically reviewed the economic evidence on the cost-effectiveness of in-person CBT for psychosis in adults with schizophrenia. In studies that compared usual care with CBT for psychosis provided by specifically trained nonphysician therapists, CBT for psychosis represented good value for money.[23,30]

All examined studies were patient-level economic analyses conducted as part of randomized controlled trials with up to 18 months of follow-up after interventions provided for 9 to 12 months. They included a mixed population of adults with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, or early psychosis) and, in one study,[23] also people with bipolar psychosis. However, most trials excluded people with addictions or those unable to communicate in the country's official language; hence, generalizability of the benefit of CBT for psychosis to certain specific and at-risk populations is limited.

Most of the studies were conducted in adults with treatment-resistant disease, but no study examined the cost-effectiveness of CBT for psychosis long-term, initiated at a first-episode and continued in relapse, mimicking the usual lifelong course of schizophrenia. Although numerous reviews and guidelines have recommended continuing with CBT for psychosis at various stages of schizophrenia,[8,10,16,28,70,71] the cost-effectiveness of long-term provision of this therapy remains unexplored. In addition to these methodological limitations, none of the included studies were conducted in Canada.

Conclusions

Our review showed that a small number of cost-utility analyses have examined the incremental value of CBT for psychosis versus usual care in adults with schizophrenia. These patient-level economic evaluations suggested that individual or group CBT for psychosis, delivered in-person for 9 to 12 months, represented good value for money. However, these findings cannot be generalized to Ontario's health care system because of differences in health care resource use and the organization of psychiatric care among the countries. Moreover, the lack of evidence on the cost-effectiveness of CBT for psychosis for the long-term management of schizophrenia in adults provided additional reasons for us to conduct a primary economic evaluation for Ontario.

PRIMARY ECONOMIC EVALUATION

The published economic evaluations identified in our literature review addressed the interventions of interest but had several methodological limitations (e.g., selected study populations, short-term time horizons, limited information on the long-term cost-effectiveness of CBT for psychosis including recurrent psychotic episodes). Also, none of these published studies took an Ontario perspective. Therefore, we conducted a primary economic evaluation.

Research Question

What is the incremental cost-effectiveness of cognitive behavioural therapy (CBT) for psychosis combined with usual care, compared with usual care alone, in adults with newly diagnosed schizophrenia in Ontario, where CBT for psychosis is delivered by psychiatrists or certified, regulated nonphysician therapists (e.g., psychologists)?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement (CHEERS).[72] The methodological approaches follow the recent recommendations of the fourth edition of the Canadian Agency for Drugs and Technologies in Health (CADTH) Guidelines for the Economic Evaluation of Health Technologies[73] and align with Health Quality Ontario's Health Technology Assessments Methods and Process Guide.[74]

Type of Analysis

We conducted cost-effectiveness and cost-utility analyses. In the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) was expressed as the incremental cost per clinically relevant effectiveness outcome: for example, the cost per relapse avoided or cost per life-year saved. In the cost-utility analysis, the ICER was expressed as the cost per one quality-adjusted life-year (QALY) gained. A QALY is a measure that jointly accounts for changes in both quantity and quality of life (morbidity).[75]

Target Population

Our study population was adults aged 18 years or older with a newly diagnosed first-episode of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and considered eligible for CBT for psychosis.

Schizophrenia is a complex chronic mental disorder that usually presents in young adults between 16 and 30 years of age. The prevalence is greater in men; people with schizophrenia are also at an increased risk of substance use, homelessness, and unemployment.[3,4,76-78] To model equitable access to CBT for psychosis, we considered all patients to be eligible for this treatment regardless of their ethnicity, ability to speak or understand English, or history of substance use.[22,27,28] The only population not considered eligible for CBT for psychosis was people with severe learning disabilities who would not able to engage in CBT.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions and Comparators

We compared CBT for psychosis, provided by regulated nonphysician therapists or by physicians trained in delivering this therapy, with usual care for adults with schizophrenia. In the background section of this report, we described CBT for psychosis in general: its components, indications, and delivery formats. Here, we continue with describing strategies used in our economic model, as developed in consultation with experts throughout the development of this health technology assessment.

Modeling Optimal Delivery of CBT for Psychosis in Ontario

In line with the current guidelines, we assumed CBT for psychosis would be delivered in addition to usual care.[8,10,28] Through expert consultations, we arrived at a delivery model with two levels of care and two categories of service providers, to optimize the provision of CBT for psychosis in Ontario. In our model, CBT for psychosis is delivered by physicians and by nonphysicians (nonphysicians already offer this therapy in a few academic mental health clinics in Toronto). And, in keeping with the 2017 Canadian guidelines,[28] it was also important to have CBT for psychosis available to support people in all stages of schizophrenia: in first-episode psychosis, in relapse, and in treatment-resistant disease. This aim is represented by two levels of treatment (first-episode and relapse), described further, below.

Table 7 summarizes the strategies evaluated in the economic model:

- CBT for psychosis provided by physicians (in addition to usual care)
- CBT for psychosis provided by nonphysicians (in addition to usual care)
- Usual care alone

Table 7: Interventions and Comparators Evaluated in the Primary Economic Model

Interventions	Comparator	Patient Population
CBT for psychosis in a two-level approach, in addition to usual care: ***Care by physicians*** Level 1 (first-episode psychosis): • Individual format (100%): 16 sessions, 1-hour weekly Level 2 (relapse): • Individual format (100%): 24 sessions, 1-hour weekly	**Usual care**[a]: No CBT for psychosis Pharmacotherapy Inpatient, outpatient and community mental health services	People with schizophrenia: first-episode psychosis or recurrent disease
Care by nonphysicians Level 1 (first-episode psychosis)[b]: • Individual format (47%): 16 sessions, 1-hour weekly • Group format (53%): 16 sessions, 1.5-hour weekly, 2 clinicians, 12 participants Level 2 (relapse): • Individual format (100%): 24 sessions, 1-hour weekly	**Usual care**[a]: No CBT for psychosis Pharmacotherapy Inpatient, outpatient and community mental health services	People with schizophrenia: first-episode psychosis or recurrent disease

Abbreviations: CBT, cognitive behavioural therapy.
[a]In the reference case analysis, usual care was assumed to be delivered uniformly to all patients, as per Canadian guidelines recommendations.[8,21]
[b]The probability of people getting individual CBT for psychosis was tested in sensitivity analysis, in a scenario assuming that 100% of patients start with a group format.

In our decision-analytic model, the course of therapy starts after the acute phase of first-episode psychosis when people are stabilized and able to engage in CBT for psychosis.

We assumed that physicians providing CBT are psychiatrists. It is not known whether any psychiatrist in Ontario currently holds group sessions for CBT for psychosis in publicly funded settings. Given issues with the feasibility of providing group CBT for people with schizophrenia in Ontario where access to psychiatric treatment is limited, we assumed, after consultations with experts, that psychiatrists would provide CBT for psychosis only through individual sessions.

Level 1 treatment consists of one course of CBT for psychosis delivered using a structured approach and an individual format or, for certain patient populations, a group format. Group therapy is delivered by nonphysicians. Level 2 treatment consists of additional sessions of CBT in an individual format, mainly for people experiencing relapse or treatment-resistant disease.

Our definition of a two-level approach is slightly different from the stepped-care model recommended by the National Institute for Health and Care Excellence (NICE) for treatment of depression and anxiety.[79] The NICE approach includes the use of unregulated health care professionals in the first-step delivery of CBT and does not specify the intensity of CBT delivery in terms of an increasing number of sessions. Our approach accounts for an increasing number of sessions and a change in delivery format as the disease progresses, and the therapy is always delivered by regulated health care professionals with extensive training in CBT for psychosis.

Below, we describe our two-level approach in more detail.

Level 1: Group or Individual Format, Structured Approach to CBT for Psychosis

- All patients were assumed to be stabilized after the acute phase of first-episode psychosis
- Approximately 53% of individuals were assumed to undergo the first course of CBT for psychosis in group therapy. The rest (47%[76]) were assumed to have substance use disorder and not be able to engage in group psychotherapy; thus, they would receive individual CBT for psychosis
- Sessions were assumed to run weekly for approximately 4 months—a total of 15 sessions and 1 booster session—for both group and individual formats
- Group CBT for psychosis was assumed to be delivered by 2 clinicians: a highly skilled, trained clinical psychologist (with supervisory experience) and another, less experienced therapist (e.g., social worker, psychologist in training, case manager)
- Group sessions were assumed to have 8 to 12 people and last 1.5 hours
- Individual sessions, lasting 1 hour, were assumed to be provided by a trained, regulated, certified health care professional (clinical psychologist or psychiatrist)
- A structured approach to therapy was assumed for all level 1 sessions, whether group or individual
- In a scenario analysis, we also tested the value of a brief, low-intensity structured course of CBT for psychosis consisting of 6 to 10 individual sessions plus 2 booster sessions, provided to all eligible patients by a regulated, certified CBT therapist;[53] these sessions were assumed to be delivered weekly and to last 1 hour

Level 2: Individual Format, Formulation-Based CBT for Psychosis

- All patients were assumed to either have relapse or treatment-resistant disease
- In discussions with clinical experts, the triggers to refer a patient to level 2 CBT for psychosis were determined to be the following: no improvement in symptoms with the first course of CBT, relapse, or treatment-resistant disease (clinical experts, personal communication)

- Level 2 CBT for psychosis was assumed to be delivered one-to-one (no group therapy) by a certified, experienced clinician (e.g., a clinical psychologist with supervisory experience or a psychiatrist)
- Sessions were assumed to run for approximately 6 months, in 1-hour weekly sessions for 24 weeks
- The approach to CBT for psychosis at this level was assumed to be formulized (determined by the therapist based on the patient's symptoms) on a case-by-case basis

Modeling Usual Care Including Pharmacotherapy

Our research objective was to determine the incremental cost-effectiveness of CBT for psychosis plus usual care over usual care alone; we simplified the modeling of pharmacotherapy for schizophrenia as suggested by our clinical experts, by using several uniform treatment pathways and triggers for switching drugs. Table 8 presents our approach to the modeling of pharmacotherapy switch and the corresponding pathways for treatment monitoring, such as frequency of follow-up. We used risperidone and quetiapine at their recommended doses as these second-generation antipsychotics (SGAs) are commonly prescribed in Ontario.[80,81] Treatment switch was initiated as a result of nonresponse, relapse, severe side effect, or patient preference at probabilities shown in the literature.[82-88] Treatment-resistant schizophrenia was defined as a state with persistent, clinically significant positive symptoms after 2 adequate trials of SGAs. In this state, patients were switched to clozapine for at least 8 weeks.[9]

All these medications are associated with difficult side effects such as extrapyramidal symptoms (e.g., tremors and spasms similar to Parkinson disease) and hyperprolactinemia (an abnormal increase in production of the hormone prolactin, causing problems with breast swelling or tenderness). Therefore, our model included regular follow-up visits to monitor people, reassess, and change treatment if necessary.[7-9] For people on clozapine, we modeled regular lab testing to monitor for agranulocytosis (a severe shortage of white blood cells with risk of potentially fatal infections), a dangerous side effect of clozapine that occurs in 1% to 2% of patients.

Table 8: Modeling Pharmacotherapy as Part of Usual Care

Health States	Medication, Dosage, Duration[a]	Major Side Effects[b]	Follow-up[c]	Reasons for Medication Switch
First episode: acute stabilization and maintenance phases	SGA, 1st line: risperidone 2–8 mg /day 2 years	Weight gain EPS HPRL[d] Sedation	Initial: at 4 weeks 2nd: at 8 weeks Regular: every 3 months[e]	Nonresponse Intolerable side effect Patient preference
Relapse: acute stabilization and maintenance phases	SGA, 2nd line: quetiapine 300–750 mg/day 2 years	Weight gain EPS[f] HPRL[d] Sedation	Initial: at 4 weeks 2nd: at 8 weeks Regular: every 3 months[e]	Nonresponse Intolerable side effect Patient preference
Treatment-resistant schizophrenia[g]	Clozapine 300–800 mg/day 2 years	Weight gain EPS[d] HPRL[d] Sedation Agranulocytosis	Initial: at 4 weeks 2nd: at 8 weeks 3rd: at 16–18 weeks Regular: every 3 months[e]	Nonresponse Intolerable side effect Patient preference

Abbreviations: EPS, extrapyramidal symptoms; HPRL, hyperprolactinemia; SGA, second-generation antipsychotics.

[a]Range of dosage includes changes in the medication dose from the beginning of treatment, during optimization until the maintenance phase, with optimal duration of treatment as recommended by the guidelines.[9,10]

[b]Side effects considered in the model and medications used to alleviate them.

[c] Monitoring people on SGAs is assumed to be more frequent for the first 2 months; for clozapine, monitoring is assumed to be more frequent for the first 4.5 months due to the possibility of severe side effect (agranulocytosis) after approximately 18 weeks of treatment.[10,88]

[d]Medication to treat HPRL is assumed to be bromocriptine, 5 mg/day.

[e]Regular follow-up with a psychiatrist, assuming no treatment discontinuation.

[f]Medication to treat EPS is assumed to be apo-benztropine, 4 mg/day.

[g]Patients fail (have persistent significant positive symptoms) after 2 trials of SGAs.[9,10,19]

Outcomes of Interest

- Effectiveness outcomes: number of recurrent episodes (relapses), number of suicides, number of hospitalizations, life-years (overall survival), and QALYs
- Direct medical costs
- Incremental cost-effectiveness and cost-utility ratio ratios (ICERs): cost per life-year saved and cost per one QALY gained

Discounting and Time Horizon

As suggested by the CADTH guidelines,[73] we applied an annual discount rate of 1.5% to both costs and QALYs in the reference case analysis. We used a 5% discount rate in sensitivity analysis. All costs are expressed in 2017 Canadian dollars.[89]

The time horizon for the reference case analysis was 5 years. Due to the episodic nature of schizophrenia, we deemed a 5-year time horizon was long enough to capture initial and downstream costs associated with initial and repeated courses of CBT for psychosis and costs of additional therapies related to overall management of the disease. The short-term time horizon was also chosen for the reference case as no long-term evidence exists on the efficacy of CBT for psychosis in people with schizophrenia. Longer time horizons were examined in sensitivity analysis (e.g., 10 years, lifetime, or until age 100 years).

Model Structure

We developed a state-transition (Markov) probabilistic microsimulation (individual-level) model to evaluate CBT for psychosis in addition to usual care, compared to usual care alone, for a

hypothetical cohort of women and men aged 18 years and older and diagnosed with a first episode of psychosis. The model simulation starts in the stabilizing phase (with continuation of the treatment with risperidone initiated in the acute phase) at which the severity of a patient's symptoms was assumed to be at a level that would not prevent their engagement with CBT therapy. We tracked overall survival, quality-adjusted survival, number of relapses, number of hospitalizations, number of deaths as a result of suicide, treatment switches, and direct medical costs over the first 5 years following a person's diagnosis of schizophrenia in the reference case, and over longer time frames in sensitivity analysis, as noted.

Drug switch was carefully modeled using tracker (counter) variables to flag reasons for discontinuation of the SGA treatment and to count the number of SGAs used or the number of courses of CBT. The counter variable was used to flag and model increased risks of second and next relapse after treatment discontinuation. Transitions of people from one health state to another could occur each week; this is called a model cycle. We applied a technique known as the half-cycle correction to balance the distribution of people who transition between health states at the beginning or end of each cycle.[90]

We used this short weekly cycle to monitor changes in the progression of disease and adequately reflect what is seen and done in current clinical practice:

- Dropout (and its consequences) during each course of CBT for psychosis
- SGA switches due to severe side effects and introduction of additional drugs to manage side effects
- Changes in risks of hospitalization or death with different health states and in correlation to complications from the use of SGAs
- Temporal changes in disutility resulting from drug side effects

As presented in Figure 3, the model simulated the course of schizophrenia through a series of transitions among different Markov health states.

- **First-episode psychosis**, **stabilizing phase of schizophrenia**, after 8 weeks of treatment with SGA #1: in this state the first course of CBT for psychosis (level 1) is delivered
- **Stable, in remission** and on SGA #1 or SGA #2, with or without complications (diabetes, coronary heart disease): these are 4 different health states and no CBT for psychosis is provided in any of them
- **Relapse** with acute psychosis lasting up to 8 weeks: this health state can count and track up to 2 relapses, with a drug switch from SGA #1 to SGA #2 and then to clozapine
- **Relapsed, stable on drugs and in stabilising phases**: people transition to this state directly from the prior health state after 8 weeks of therapy. In this health state, the second course of CBT for psychosis is delivered (level 2, individual therapy)
- **Treatment-resistant disease:** this health state occurs after patients fail 2 trials of different SGAs. It could include people with or without prior complications, based on their prior history ("remembered" using tracker variables). In this health state, the third course of individual CBT for psychosis (level 2) can be delivered
- **Unstable schizophrenia:** in this health state, people have discontinued treatment, with the presence of positive and negative symptoms, and they consequently have an increased risk of death and complications (if these occurred in previous health states)
- **Death:** this is an absorbing health state, from which no transition to another state is made

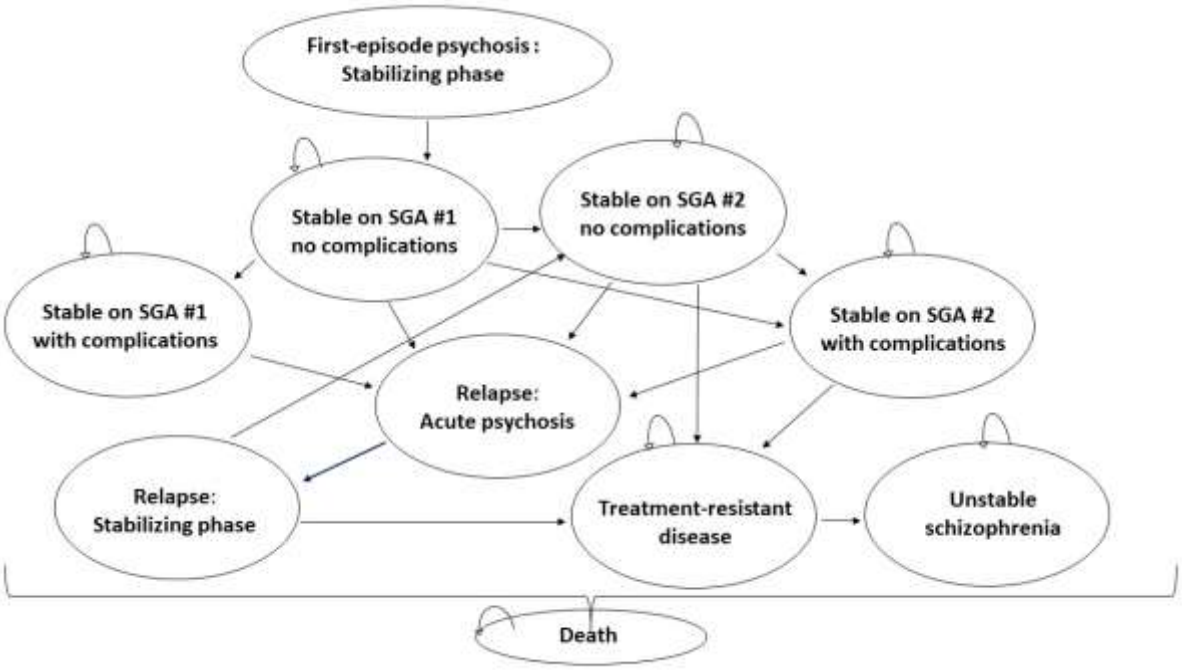

Figure 3: Model Structure Schematic

Abbreviation: SGA, second-generation antipsychotic.

This figure depicts an individual-level (microsimulation) Markov model that includes 10 health states, each represented by an oval. In each 1-week cycle, a patient has a chance to move among health states. Death is an absorbing Markov health state from which no further transition is made. The simulation starts with a hypothetical patient aged 18 years with first-episode psychosis in the stabilizing phase during which they engage in CBT for psychosis (level 1, 16 sessions). During this treatment, a patient may drop out and be hospitalized for relapse. The model flags each relapse to account for an increased risk of another psychotic episode and for switch in drug treatment. Drug switches are also flagged using tracking variables; drug switches depend on patient compliance, side effects, and nonresponse to therapy. The probabilities of side effects are modeled in the drug health states (SGA #1 and SGA #2). The risks of severe complications (diabetes and coronary heart disease) from metabolic syndrome are accounted for in separate health states (e.g., Stable on SGA #1 with complications). Patients transfer to the treatment-resistant disease health state if they fail SGA #1 and SGA #2 (i.e., two trials of antipsychotics). From this state, people may discontinue all treatment and transfer to the unstable disease state with increased risks of suicide and death from other causes due to unstable untreated symptoms.

Main Assumptions

- Based on the results of our clinical review, we assumed that the efficacy of CBT for psychosis did not depend on the number of sessions and was not different between types of providers or therapy formats
- We assumed that the treatment-related utility of CBT for psychosis was sustained during the course of therapy for up to 2 years, supported by the evidence from our economic review[23,30,91]
- Based on the results of our clinical review, we modeled the efficacy of CBT for psychosis in preventing relapse as time-dependent; the model includes short-term and long-term effects of therapy (risk of relapse)
- No side effects of CBT for psychosis were included in the model, based on the results of our clinical review and lack of evidence in this area
- The cost of training less experienced therapists in CBT for psychosis was included in their salary, assuming that the training was part of their achieving competency during a year of work under supervision; this assumption is in accordance with the current delivery of CBT for psychosis in Ontario (clinical experts, personal communication)

- Usual care, including medications and inpatient and outpatient mental health services, was assumed to be delivered uniformly to all patients, as described in Table 8 and in agreement with Canadian guidelines recommendations[7,8]
- Medication switch occurred after nonresponse or severe side effects
- People who discontinued SGA #1 switched to SGA #2, and if they failed both SGAs, they were switched to clozapine. If they failed all treatments, they transitioned to the unstable disease health state
- No drug holiday was modeled
- Dropout could occur at any stage of CBT for psychosis
- People who attempted suicide were assumed either to die or to survive and be hospitalized
- In accordance with the literature and clinical course of schizophrenia, people with metabolic syndrome were assumed to be at risk for developing diabetes and cardiovascular complications
- In the unstable disease health state, we modeled an increased risk of death and a risk of relapse attributable to untreated disease, including all relevant utilities and costs of ongoing complications; we assumed no CBT for psychosis was delivered in this health state

Clinical Outcome and Utility Parameters

We used a number of different input parameters to populate the model. Parameters related to the natural history of schizophrenia were used to describe the course of newly diagnosed and recurrent episodes of psychosis, including factors affecting the risk of recurrence such as discontinuation of medications due to patient preference or side effects, number of relapses, risk of suicide and hospitalizations, and risks of complications of metabolic syndrome including diabetes and coronary heart disease. To estimate the incremental cost-effectiveness of CBT for psychosis against usual care, we populated the model with parameters related to the efficacy of CBT for psychosis, health state utilities, and costs.

Natural History

Schizophrenia has both a chronic and episodic nature, worsening and improving by varying degrees. People with schizophrenia have an increased risk of having other psychiatric conditions, such as substance use disorders (approximately 47%).[76] Relapse (treatment failure and recurrence of acute psychotic episode) is quite common among people with either first-episode psychosis or established chronic disease. Around 80% experience a relapse within 5 years of a treated first-episode psychosis.[2]

Table 9 presents all input parameters used to populate the Markov individual-level model for the use of CBT for psychosis in people with schizophrenia. Our model simulates the chronic, episodic course of the disease in patients receiving usual care including antipsychotic medication. It begins with a person in the stabilizing phase of the disease. Based on an implementation study in Ontario,[92] a meta-analysis of 115 studies,[93] and expert opinion, we accounted for a dropout rate of 25% among people receiving CBT for psychosis.

Next, based on the analysis of the CATIE trial,[94,95] as suggested in an economic analysis by Park et al,[88] we modeled the probabilities of relapse, therapy discontinuation, adverse effects of antipsychotic drugs (risperidone, quetiapine, clozapine), and metabolic syndrome including risks

of its complications (diabetes, coronary heart disease). Other rates of relapse suggested by various authors were tested in sensitivity analysis.[2,96]

Based on a study by Robinson et al,[2] which found that discontinuing medication was the only factor to significantly affect the prognosis of schizophrenia in people with first-episode psychosis, we modeled an increase in the risk of next relapse after people stopped their antipsychotic medication.

People with schizophrenia have life expectancy at least 15 to 20 years shorter than the general population.[6,97,98] We accounted for excess mortality due to schizophrenia, suicide, or an uncommon adverse effect of clozapine based on data from population-based studies and a systematic review.[69,88,99-101] In scenario analyses, we incorporated findings from a recent population-based study by Tiihonen et al[99] suggesting a 25% to 57% decrease in the risk of overall mortality and mortality due to suicide after exposure to antipsychotic therapy.

Table 9: Natural History Inputs Used in the Economic Model

Model Parameter	Mean	Distribution	Source
Probabilities/Rates			
Probability of drug abuse in patients with schizophrenia	0.47	NA	Crockford and Addington, 2017[76]
Probability of drop out during CBT for psychosis, group format	0.25	NA	Expert opinion, Fischler et al, 2016[92]; Fernandez et al, 2015[93]
Probability of discontinuing drug due to nonresponse, 18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.249		
• Quetiapine	0.249		
• Clozapine	0.066		
Probability of discontinuing drug due to intolerable side effects, 18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.168		
• Quetiapine	0.287		
• Clozapine	0.374		
Probability of discontinuing drug due to patient's decision, 18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.113		
• Quetiapine	0.151		
• Clozapine	0.057		
Probability of relapse, 18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.072		
• Quetiapine	0.104		
• Clozapine	0.042		
Probability of EPS, HPRL, respectively,18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.018, 0.079		
• Quetiapine	0.009, 0.054		
• Clozapine	0.016, 0.040		

Model Parameter	Mean	Distribution	Source
Probability of metabolic syndrome, 18-week cycle[a]:		Beta[c]	Park and Kuntz, 2014[88]
• Risperidone	0.075		
• Quetiapine	0.061		
• Clozapine	0.151		
Probability of treatment switch due to serious side effects:		NA	Heeg et al, 2008[82]
• EPS	0.70		
• Weight gain	0.50		
• Diabetes	0.90		
Annual probability of developing diabetes from metabolic syndrome	0.046	Beta[c]	Park and Kuntz, 2014[88]
Annual probability of developing coronary health disease from metabolic syndrome	0.018	Beta[c]	Park and Kuntz, 2014[88]
Background mortality rate	Ontario life tables	Time- and age-dependent	Statistics Canada, 2009–2011[102]
Rate of suicide in general population	0.000166		Khan et al, 2003[101]
Increased risk of suicide in schizophrenia, standardized mortality ratio	27.94		Park and Kuntz, 2014[88]; Brown et al, 2000[100]
	12.86[b]		Saha et al, 2007[69]
Increased rate of death from agranulocytosis (clozapine)	0.00012		Park and Kuntz, 2014[88]
Risks	**Risk Ratio (95% CI)**	**Distribution**	**Source**
Relative risk of relapse after stopping medication, compared with those who continued:		Normal[c]	Robinson et al, 1999[2]
• 1st relapse	4.89 (2.49–9.60)		
• 2nd relapse	4.57 (1.42–14.02)		
Excess mortality in schizophrenia, nonstable state, after failing clozapine, compared with general population	1.23 (1.19–1.30)	Normal[c]	Park and Kuntz, 2014[88]
Excess mortality in schizophrenia		Normal[c]	
• Due to diabetes	2.19 (1.26–3.79)		Park and Kuntz, 2014[88]; Leibson et al, 2005[103]
• Due to coronary heart disease	1.67 (1.05–2.66)		Park and Kuntz, 2014[88]; Nabi et al, 2010[104]
Decrease in risk of death at 5 years, with exposure to antipsychotics[c]		Normal[c]	Tiihonen et al, 2016[99]
• Overall mortality	0.75 (0.63–0.89)[b]		
• Mortality due to suicide	0.43 (0.24–0.78)[b]		

Abbreviations: CBT, cognitive behavioural disorder; CI, confidence interval; NA, not applicable; EPS, extrapyramidal symptom; HPRL, hyperprolactinemia.

[a]Probability recalculated for 1-week cycle.

[b]Used in sensitivity scenario analysis only.

[c]Distributions assigned in probabilistic sensitivity analysis; normal distributions assigned to log-odds ratios.

Intervention Effects

The effectiveness of CBT for psychosis on decreasing the risk of recurrence of psychotic episodes over time is uncertain. A systematic review by Jones et al,[49] described in our clinical evidence review, reported the effects of CBT for psychosis (in addition to usual care) on the short-term and long-term risks of relapse, hospitalization, and death. For each of these outcomes, this systematic review assessed between 1 and 5 studies with a combined 71 to 350 patients with schizophrenia. We used data from this study to inform input parameter values for our decision-analytic model that accounted for short-term and long-term effectiveness of CBT for psychosis on several important clinical outcomes (Table 10).

Our clinical review also identified two systematic reviews[46,52] that included studies in patients with first-episode psychosis who attended early-psychosis programs and were assessed for risk of relapse with CBT for psychosis. The risk of relapse with CBT for psychosis compared with other types of psychological therapies in this patient population was similar to that reported by Jones et al.[49]

Lastly, we modeled the same efficacy for group and individual formats of CBT for psychosis. This is consistent with findings of our clinical review which found two studies that evaluated differences in the effects of group versus individual psychotherapy, using meta-regression or subgroup analyses.[54,57] Both analyses showed no significant difference in target symptoms between individual and group CBT for psychosis; however, none of the subgroup analyses were explicitly defined a priori or did not have statistical power to show significant differences between the effects of group and individual CBT for psychosis.

Table 10: Summary Effectiveness Estimates Used in the Economic Model

Model Parameter	Relative Risk (95% CI)	Distribution[a]	Source
Risk of relapse, end of treatment: CBT for psychosis vs. usual care	0.65 (0.21–1.95)	Normal	Jones et al, 2012[49]
Risk of relapse, follow-up: CBT for psychosis vs. usual care	0.91 (0.63–1.32)	Normal	Jones et al, 2012[49]
Risk of rehospitalization, long-term: CBT for psychosis vs. usual care	0.86 (0.61–1.20)	Normal	Jones et al, 2012[49]
Risk of death: CBT for psychosis vs. usual care	0.57 (0.12–2.60)	Normal	Jones et al, 2012[49]

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval.
[a]Normal distributions assigned to log-odds ratios.

Health State Utilities

Table 11 presents the health state utilities used in our analysis to calculate quality-adjusted life-years (QALYs). A QALY is a measure that jointly accounts for changes in both quantity and quality of life (morbidity).[75] A health state utility is a measure of health-related quality of life and reflects the strength of preference for specified health states. By convention, health state utilities are anchored on death and best possible health (death is assigned a utility weight of 0, and perfect health is assigned a utility weight of 1).[75] The value of a QALY for a certain health state is calculated by multiplying time spent in that health state with the utility assigned to that health state (e.g., 1 year of untreated schizophrenia with a utility weight of 0.4 equals a QALY of 0.4).

We performed a targeted literature search using MEDLINE (Ovid interface) on April 6, 2017, for studies published from inception to the search date to determine changes in health state utilities with the intervention. The search was based on the clinical search strategy with a methodological filter applied to limit retrieval to health state utility values. See Appendix 1 for literature search strategies, including all search terms.[64,65] Two studies indicated changes of 0.03 to 0.04 QALYs after the application of therapy, up to 18 months after the course of CBT for psychosis.[23,30,91] For the reference case, we used estimates from a study by Barton et al[23,91] that calculated change in utilities after CBT for psychosis using the EQ-5D (a questionnaire that captures health-related quality of life) in 77 patients with schizophrenia. We further tested these input values in scenario analysis. Other utility weights relevant to schizophrenia-specific health states and medication-related adverse effects were derived from a systematic review of studies reporting quality of life and utilities in patients with schizophrenia[105] and from published pharmacoeconomic modeling studies and guidelines.[83,84,88,106-110]

Table 11: Health State Utilities Used in the Economic Model

Model Parameter: Utilities	Mean (SE)	Distribution	Source
Acute psychotic episode, untreated schizophrenia	0.676 (0.037)	Beta	Barton et al, 2009[91]
Stable, treated schizophrenia, no adverse effects			
SGA #1 and SGA #2	0.92 (0.023)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
Treatment-resistant disease	0.820 (0.031)	Beta	Mavranezouli, 2010[105]; Oh, 2001[109]
CBT-treated schizophrenia, change in utility from baseline, addition to SGA			
9 months	+0.043 (0.039)	Beta[a]	Barton et al, 2009[91]
18 months	+0.043 (0.039)	Beta[a]	Barton et al, 2009[91]
Nonstable state, schizophrenia	0.42 (NR)	Beta	Lenert et al, 2005[110]
Relapse	0.604 (0.042)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
Diabetes (schizophrenia)	0.769 (0.036)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
Coronary heart disease (schizophrenia)	0.769 (0.036)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
EPS (schizophrenia)	0.722 (0.037)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
HPRL (schizophrenia)	0.815 (0.025)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]
Weight gain (schizophrenia)	0.825 (0.028)	Beta	Briggs et al, 2008[106]; Mavranezouli, 2010[105]

Abbreviations: CBT, cognitive behavioural therapy; EPS, extrapyramidal syndrome; HPRL, hyperprolactinemia; NR, not reported; SE, standard error; SGA, second-generation atypical antipsychotics.

[a]CBT treatment-related utility was added to the utility of a health state in which CBT was delivered, and the beta distribution was assigned to the overall estimate.

Cost Parameters

We estimated the direct medical costs associated with the model strategies using the cost estimates presented in Table 12.

The costs of CBT treatment consisted of the following costs:

- Initial assessment, including the cost of the visit to a general practitioner to obtain a specialist referral, plus the cost of the visit during which a psychiatric assessment is conducted by a psychiatrist or psychologist
- Professional services by a publicly funded, regulated health care provider to deliver CBT for psychosis

As outlined in the Interventions and Comparators section, above, we modelled a two-level approach to delivery CBT for psychosis (Table 7). Level 1 (in the stabilizing phase of first-episode psychosis) consists of 16 sessions delivered as individual therapy (1 hour a week to 1 person by 1 therapist) or as group therapy (1.5 hours a week to a group of 12 people by 2 therapists). Level 2 (after relapse) consists of 24 weekly sessions, delivered as individual (1 person, 1 therapist) 1-hour sessions. All therapy is face-to-face and delivered either by psychiatrists or regulated mental health therapists. Therefore, we calculated the costs of professional services to deliver CBT for psychosis as the product of the number of sessions and the applied hourly salary (for nonphysicians) or fee-for-service costs (for physicians), adjusted for the length of sessions (1 hour for individual versus 1.5 hours for group).

Next, we explain how we calculated labour costs for nonphysicians after adjustment for clinical work. In the reference case analysis, we used the unit costs associated with the highest applied hourly rates estimated for a publicly funded, certified, experienced nonphysician professional (i.e., a regulated clinical psychologist with supervisory experience in leading group therapy in CBT for psychosis).

We estimated the salary ranges of publicly funded, regulated therapists (e.g., psychologists, occupational therapists, psychotherapists, and social workers) from published data[111-115] and expert consultation. The average annual salary for publicly funded, registered therapists ranges from $110,000 to $130,000, with benefits ranging from 17% to 30%.[115,116] Based on expert opinion, we assumed that one of the two clinicians providing group CBT for psychosis (level 1) would be a therapist in training, with an annual salary of $35,000.

To estimate the labour costs associated with clinical activities, we calculated an applied hourly salary. Applied cost recognizes that clinicians spend time on nonpatient activities, so less than 100% of a clinician's time accounts for clinical work.[117] Using an applied rate of 85%, we calculated applied hourly salaries for publicly funded therapists for our base case and scenario analyses. This is a recognized applied rate for medical staff; a similar number of hours per year has been used in labour cost estimations.[117] The following provides an example of our calculations:

- A full-time equivalent (FTE) employee works 1,950 hours per year (assuming 7.5 hours per day, 5 days per week, and 52 weeks per year)
- Using the applied rate of 85%, the applied time is thus 1,950 × 0.85 = 1,658 hours per year
- Given an annual salary of $130,000 with 30% benefits for an experienced therapist (for a total of $169,000 per year), the applied hourly cost is thus $169,000 ÷ 1,658 = $101.93

- Given an annual salary of $35,000 with 30% benefits for an in-training therapist (for a total of $45,500 per year), the applied hourly cost is thus $45,500 ÷ 1,658 = $27.44

We based the costs of follow-up by physicians on the fee-for-service schedule and number of visits related to pharmacotherapy (Table 8). We assumed that:

- In first-episode or relapsed psychosis, patients would have follow-up visits with a general practitioner every month for the first year of treatment with a new medication
- Follow-up visits with a psychiatrist would have a similar pattern for the first 5 months, with follow-up visits every 3 months thereafter
- Monitoring the treatment effect of SGAs would be more frequent for the first 2 months; for patients taking clozapine, monitoring would be more frequent during the first 4.5 months due to the possibility of a severe side effect (agranulocytosis) occurring after approximately 18 weeks of treatment[9,10,88]
- Costs of treatment monitoring would change if patients discontinued their treatment

A study by Becker and Hux[118] showed that 78% of Ontarians with pre-existing schizophrenia had drug coverage in the study period of 1996 to 2005, largely through the Ontario Disability Support Program. Thus, we assumed that 78% of patients had drug coverage in our reference case analysis and that this coverage rose to 100% in a scenario analysis.

Ontario costs of drug acquisition, home care, inpatient and outpatient care, and complications due to diabetes or coronary heart disease were mainly based on data from the literature (Table 12). We based the costs of medication-specific inpatient and outpatient care including mental health care services on a modeling study conducted by Farahati et al[119] for the Canadian Agency for Drugs and Technologies in Health. They compared the cost-effectiveness of SGAs (risperidone, quetiapine, and clozapine) after accounting for resource use and services in Ontario's population.[80,120]

The reference case analysis included costs relevant to the perspective of the Ontario Ministry of Health and Long-Term Care. In a scenario analysis, we accounted for productivity losses due to morbidity and premature mortality attributable to schizophrenia as estimated using the friction cost method by Goeree et al.[121] That study estimated a total of 234,305 people with schizophrenia accounted for productivity losses of $4.83 billion dollars, for a crude estimate of $20,614 productivity lost per person in 2004.

Table 12: Estimated Per-Patient Costs Used in the Economic Model: Interventions, Usual Care, Follow-Ups, Complications, Indirect Costs

Parameter: Costs	Mean, $ (SE)[a]	Distribution	Source
CBT for psychosis (CBTp), weekly			
Initial assessment, one-time per course	223.35 (55.84)	Gamma	
GP referral visit	62.75		OHIP code: K005[122]
Assessment by psychiatrist	80.30		OHIP code: K197[122]
CBTp, provided by psychiatrist		Gamma	
Individual session (1 hour/week)	160.60 (40.15)		OHIP code: K197[122]
CBTp, provided by nonphysician[b]		Gamma	Expert consultation, literature: 1st provider, annual salary of $130,000[115]; 2nd provider in training, annual salary of $35,000 plus 30% benefits[111]
Individual session (1 hour/week)	101.93 (25.48)		
Group session (1.5 hours/week)	8.09 (2.02)		
CBTp, provided by nonphysician[b,c]		Gamma	Expert consultation, literature: 1st provider, annual salary of $130,000[112-115]; 2nd provider in training, annual salary of $35,000 plus 17% benefits[116]
Individual session (1 hour/week)	86.24 (21.56)		
Group session (1.5 hours/week)	6.62 (1.65)		
CBTp, provided by nonphysician[b,c]		Gamma	Expert consultation, literature: 1st provider, annual salary of $110,000[112-115]; 2nd provider in training, annual salary of $35,000 plus 30% benefits[116]
Individual session (1 hour/week)	91.73 (22.93)		
Group session (1.5 hours/week)	7.11 (1.78)		
CBTp, provided by nonphysician[b,c]		Gamma	Expert consultation, literature: 1st provider, annual salary of $110,000[112-115]; 2nd provider in training, annual salary of $35,000 plus 17% benefits[116]
Individual session (1 hour/week)	77.62 (19.40)		
Group session (1.5 hours/week)	6.39 (1.60)		
Pharmacotherapy			
Risperidone (annual[d])	2,007	Fixed	Farahati et al, 2007[119]
Quetiapine (annual[d])	4,071	Fixed	Farahati et al, 2007[119]
Clozapine (annual[d])	8,237	Fixed	Farahati et al, 2007[119]
Treatment monitoring, outpatient and inpatient care			
Psychiatrist, repeat consultation	105.25 (26.31)	Gamma	OHIP code: A196[122]
GP, primary care visit	62.75 (15.69)	Gamma	OHIP code: K005[122]
Laboratory ($/visit)	45	Gamma	Farahati et al, 2007[119]
• Risperidone (2 visits/year)	90 (22.5)		
• Quetiapine (2 visits/year)	90 (22.5)		
• Clozapine (52 visits/year)	2,117 (529.3)		
Acute hospitalization and follow-up (per event)	13,028 (3,257)	Gamma	McIntyre, 2010[108]
Group home care ($/day)	215	Gamma	Farahati et al, 2007[119]
• Risperidone (15% days/year)	11,745 (2,936)		
• Quetiapine (15% days/year)	11,745 (2,936)		
• Clozapine (45% days/year)	35,232 (8,808)		

Parameter: Costs	Mean, $ (SE)[a]	Distribution	Source
Adverse events and complications			
EPS, apo-benztropine 4 mg/day ($/year)	14	Gamma	Farahati et al, 2007[119]
• Risperidone (annual)[e]	2		
• Quetiapine (annual)[e]	2		
• Clozapine (annual)[e]	2		
Diabetes management, overall	4,876 (1,219)	Gamma	Farahati et al, 2007[119]
• Risperidonee	2 (0.5)		
• Quetiapinee	39 (9.8)		
• Clozapinee	99 (24.8)		
HPRL, bromocriptine 5 mg/day ($/day)	1.49	Fixed	Ontario Drug Benefit formulary[123]
Coronary heart disease (nonfatal) plus follow-up, annual	4,189 (1,047) 1,953 (488.3)	Gamma	O'Brien et al, 2003[124]; McIntyre et al, 2010[108]
Other[c]			
Indirect costs, productivity loss	24,928 (6,232)	Gamma	Goeree et al, 2005[121]

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; GP, general practitioner; OHIP, Ontario Health Insurance Plan Schedule of Benefits; SE, standard error.
[a]Original nondiscounted costs in 2017 Canadian dollars, estimated per weekly cycle; standard error based on an assumption that the mean costs vary by ± 25%.
[b]Labour costs after applied salary adjustment for a full-time professional of 1,658 hours per year.
[c]Used in probabilistic sensitivity scenario analyses.
[d]Costs of drugs based on average daily dose of 4mg/day (risperidone), 600 mg/day (quetiapine), 450 mg/day (clozapine).
[e] Based on incidence rates.

Analysis

Our reference case analysis estimated the mean expected costs, mean expected effects, and incremental cost-effectiveness ratio (ICER) of CBT for psychosis compared with usual care, using probabilistic sensitivity analysis.[73]

Probabilistic sensitivity analysis handles parameter (second-order) uncertainty and nonlinear relationships among model parameters and provides the most accurate estimate of the ICER in individual-level state transition models. Parameter uncertainty was handled by setting distributions for input model parameters (Tables 9 to 12). For example, we specified the beta distribution for utilities, the normal distribution for the effect measure of treatment efficacy (i.e., the log-odds ratio), and the gamma distribution for costs. The probabilities of recurrence or death were modelled as time- or age-dependent. We simulated 1,000 trials, each of which included 1,000 patients, to obtain the mean expected costs and effects of the compared strategies in the reference case analysis.

We also used cost-effectiveness acceptability curves to graphically present uncertainty in the ICER. These curves show the probability of one alternative being cost-effective over another across a range of willingness-to-pay thresholds ($0 to $100,000 per QALY gained).

Our sensitivity analysis consisted of 13 scenarios that were also calculated using probabilistic sensitivity analysis (Table 13). For example, we examined changes in the cost-effectiveness estimates with these changes in parameters: if group CBT for psychosis was delivered to all patients; if dropout rates increased; if the efficacy of CBT for psychosis increased by 25%; if the number of CBT sessions decreased through the use of brief, low-intensity treatment (8 to 12 sessions instead of 16); or if the salary of nonphysicians providers substantially changed.

Table 13: Sensitivity Analysis: Description of Structural and Parameter Assumptions in Probabilistic Sensitivity Analysis Scenarios

Parameter/Assumption	Reference Case Analysis	Scenario Analysis: Major Changes in Parameter Values or Assumptions
1) Delivery format for level 1 CBTp in nonphysician strategy	Individual (53%) and group (47%)	• Everyone receives individual therapy • Everyone receives group therapy
2) Risk of relapse with CBTp	RR = 0.65 (short-term follow-up), RR = 0.91 (long-term follow-up)	25% decrease in risk reduction
3) Dropout from CBTp	25%	• 2 × reference case probability • 0.5 × reference case probability
4) Utility change associated with CBTp	0.04	• 1.5 × reference case estimate • 0.5 × reference case estimate
5) Decrease in mortality after the use of SGAs	RR 1	• RR 0.75 (Tiilhonen et al, 2016[99])
6) Smaller risk of suicide in population with schizophrenia	RR 27.94	RR 12.86 (Saha et al, 2007[69])
7) Number of sessions in level 1 CBTp	16	• 8 (6 CBTp sessions plus 1 assessment and 1 booster session) • 12 (10 CBTp sessions)
8) Costs of nonphysician-provided CBTp, salary-based FTE: 1,658 hours/year	Conservative assumption: 1st provider, salary of $130,000, 30% benefits (see Table 12)	• 25% increase in salary • $130,000, 17% benefits • $110,000, 30% benefits • $110,000, 17% benefits
9) Direct medical costs	All costs	CBTp-associated costs: assessment and therapy sessions
10) Drug coverage	78%	100%
11) Indirect costs	Not included	Included
12) Discount rate	1.5%	5%
13) Time horizon	5 years	• 1 year • 10 years • Lifetime

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; FTE, full-time equivalent; RR, relative risk; SGA, second-generation antipsychotic medication.

We used both ICER and incremental net benefit (INB) estimates to indicate the cost-effectiveness of the compared strategies. A positive INB indicates that a strategy is cost-effective.

We conducted all analyses using TreeAge Pro 2017 R2.1 version (TreeAge Software, Williamstown, MA) and Excel 2013 (Microsoft, Redmond, WA).

Generalizability

The findings of this economic analysis are generalizable to adults with schizophrenia able to engage in CBT for psychosis.

Expert Consultation

From May to August 2017, we sought expert consultation on the appropriate and applicable models for providing CBT for psychosis to patients with schizophrenia in Ontario. The consultation included physicians and nonphysicians in the specialty areas of psychiatry, clinical psychology, and family medicine. The role of the expert advisors was to review the model structure and inputs to confirm that the information we used reasonably reflects the clinical context of schizophrenia and application of CBT for psychosis in Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Our economic evaluation suggests that, compared with usual care, CBT for psychosis for adults with schizophrenia provided either by regulated nonphysician therapists or by physicians probably represents good value for money in Ontario. In sections below, we present the complete results of our primary economic evaluation: the reference case analysis and sensitivity analysis.

Reference Case Analysis

Table 14 presents the differences in clinical outcomes between the compared strategies in our reference case analysis. The results of our cost-utility analyses and cost-effectiveness are shown in Table 15 and Appendix 7, Table A7, respectively.

Compared with usual care over the 5-year time horizon, CBT for psychosis provided by nonphysicians or physicians increased survival by 0.02 years (7.3 days) and reduced the number of relapses by 9%, the number of suicides by 14%, and the number of hospitalizations by 5% (Appendix 7, Table A7).

Table 14: Life Expectancy, Relapse, Hospitalization, and Suicide: Usual Care and CBT for Psychosis Strategies

	Outcomes			
Strategy	Life Expectancy, Mean (95% CrI), Years[a]	Relapses/ 1,000 Patients, Mean (95% CrI)[b]	Hospitalizations/ 1,000 Patients, Mean (95% CrI)	Suicides/ 1,000 Patients, Mean (95% CrI)
Usual care	4.69 (4.65–4.73)	943 (889–1005)	710 (682–738)	1.98 (0–5)
CBT for psychosis by nonphysician	4.71 (4.66–4.75)	853 (795–912)	672 (642–692)	1.71 (0–5)
CBT for psychosis by physician	4.71 (4.66–4.75)	853 (795–912)	672 (642–692)	1.71 (0–5)

Abbreviations: CBT, cognitive behavioural therapy; CrI, credible interval.
[a]Undiscounted overall survival.
[b]Number of first and repeated relapses.

As shown in Appendix 7, Table A7, CBT for psychosis by physicians was more costly and equally effective to the therapy delivered by nonphysicians (i.e., delivery by physicians was

dominated); consequently, it was not further considered in a sequential analysis. Compared with usual care, CBT for psychosis by nonphysicians resulted in an additional cost of $158,656 per life-year saved.

Applying the incremental changes in clinical outcomes presented in Table 14, we found that, compared with usual care, CBT for psychosis provided by nonphysicians would require an additional:

- $61 to avoid one relapse in patients with schizophrenia
- $9,237 to avoid one death by suicide
- $65 to avoid one hospitalization

In sequential cost-utility analysis ranking three strategies by increasing cost, we also confirmed that CBT for psychosis by physicians was dominated by (equally effective but more expensive than) CBT for psychosis by nonphysicians (Table 15). Compared with usual care, CBT for psychosis by nonphysicians was associated with an increased discounted quality-adjusted survival of 0.12 QALYs (95% credible interval [CrI] 0.09–0.14) and increased discounted mean costs of $2,494 (95% CrI $1,472–$3,544), yielding an ICER of $21,520 per QALY gained.

The incremental cost-effectiveness ratio of CBT for psychosis provided as individual therapy by physicians versus usual care was $47,196 per QALY gained (mean incremental QALYs: 0.12, 95% CrI 0.09–0.14, and mean incremental costs: $5,470, 95% CrI $4,429–$6,570).

Table 15: Cost-Utility Analysis, Sequential Approach: CBT for Psychosis Compared With Usual Care, Cost per QALY Gained

Strategy	Mean Costs, $[a] (95% CrI)	Mean QALYs (95% CrI)	Incremental Costs,[b] $ (95% CrI)	Incremental QALYs[c] (95% CrI)	ICER: $/QALY gained
Usual care	90,294.95 (88,126–92,496)	4.008 (3.96–4.05)			
CBT for psychosis by nonphysician	92,789.30 (90,669–94,958)	4.124 (4.08–4.16)	2,494.35 (1,472–3,544)	0.1159 (0.09–0.14)	21,520
CBT for psychosis by physician	95,765.44 (93,657–97,981)	4.124 (4.08–4.16)	2,976.15 (2,822–3,129)	0.00	Dominated

Abbreviations: CBT, cognitive behavioural therapy; CRL, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All costs in 2017 Canadian dollars. All costs and effects were discounted at 1.5%.
[b]Incremental cost = mean cost (CBT for psychosis strategy) − mean cost (usual care).
[c]Incremental effect = mean effect (CBT for psychosis strategy) − mean effect (usual care).
Note: Results may appear incorrect because of rounding.

The probability of cost-effectiveness of CBT for psychosis by nonphysician therapists was high at almost all willingness-to-pay thresholds. As shown in Figure 4, it was associated with better clinical outcomes and greater costs than usual care, with 100% of the estimated ICERs below a willingness to pay of $50,000 per QALY gained in all simulations.

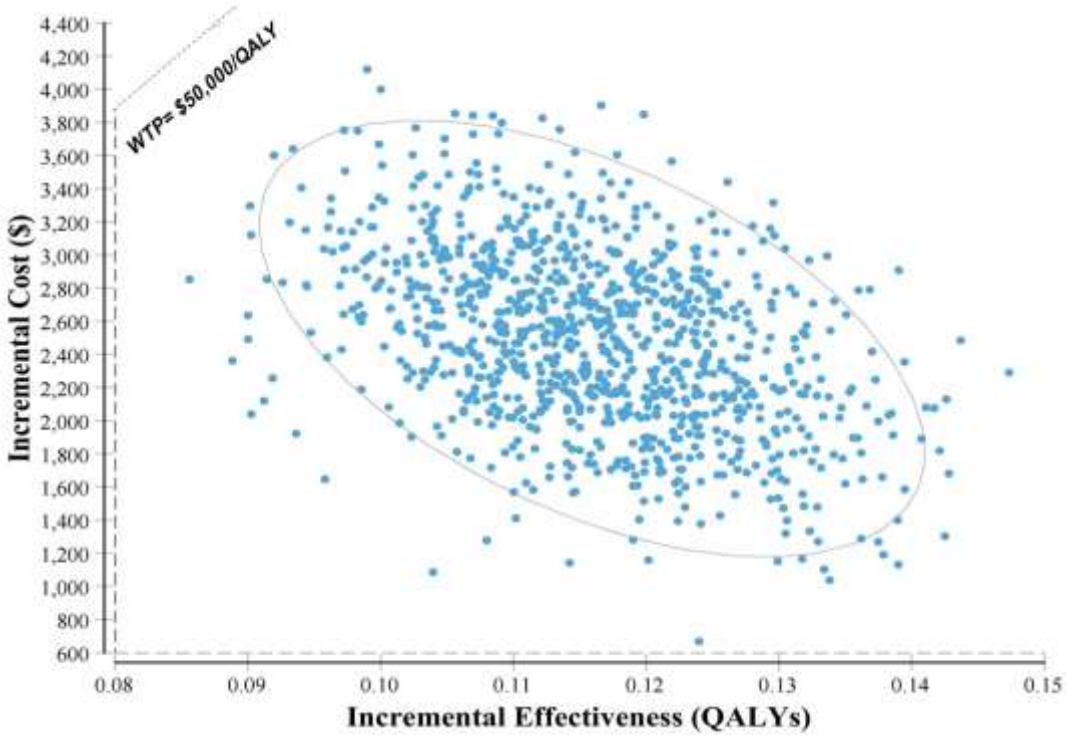

Figure 4: Scatter Plot of 1,000 Simulated Pairs of Incremental Costs and Effects in the Cost-Effectiveness Plane: CBT for Psychosis by Nonphysician Therapist vs. Usual Care

Abbreviations: CBT, cognitive behavioural therapy; QALY, quality-adjusted life-year; WTP, willingness to pay.
All costs are in 2017 Canadian dollars and discounted at 1.5%. Effectiveness is expressed in quality-adjusted life years (QALYs). The dashed line indicates a willingness-to-pay (WTP) threshold of $50,000/QALY. The incremental cost-effectiveness ratio ($21,520/QALY gained) is the slope of a straight line from the origin that passes through (0.12 QALY, $2,494) coordinate. A 95% confidence ellipse covers 95% of the estimated joint density and was used to represent uncertainty around the incremental cost-effectiveness ratio estimated in probabilistic sensitivity analysis.

On the cost-effectiveness acceptability curve, the probability that CBT for psychosis by nonphysician therapists was cost-effective compared with usual care was 72% at a willingness to pay of $25,000 per QALY, 99% at $40,000 per QALY, and 100% at any higher threshold (Figure 5).

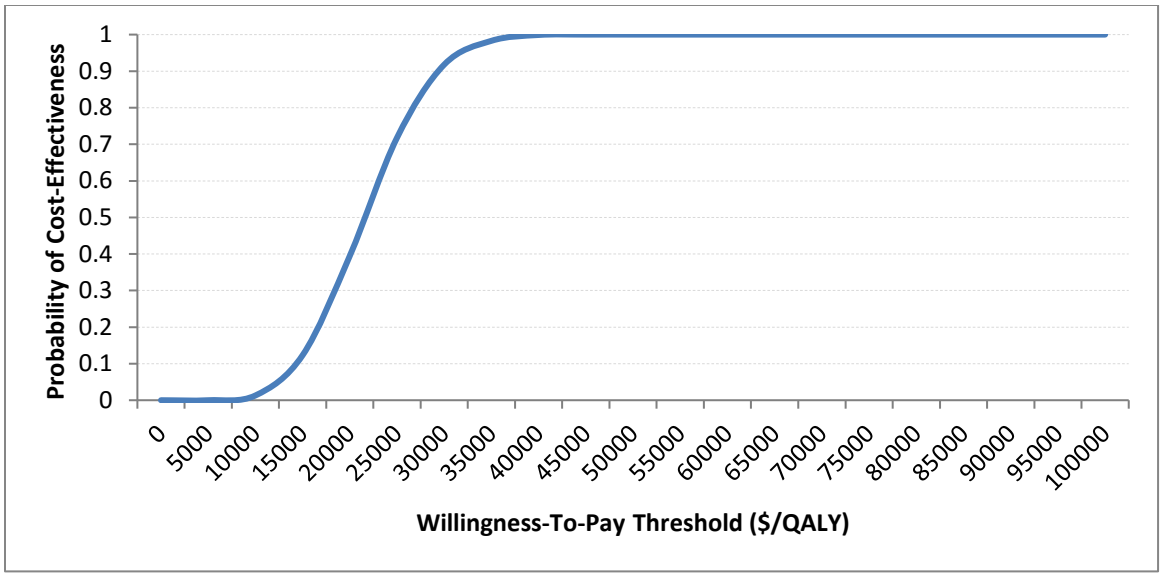

Figure 5: Cost-Effectiveness Acceptability Curve: CBT for Psychosis by Nonphysician Therapist vs. Usual Care

Abbreviations: CBT, cognitive behavioural therapy; QALY, quality-adjusted life-year; WTP, willingness to pay.
The cost-effectiveness acceptability curve (CEAC) graphically presents the probability of cost-effectiveness (blue line) of the examined CBT for psychosis strategy vs. usual care across various willingness-to-pay thresholds on the x–y coordinate system. The x-axis shows the probability of cost-effectiveness (range: 0 to 1) and the y-axis represents willingness-to-pay thresholds (range: $0 to $100,000 per one QALY gained).

When comparing CBT for psychosis by physicians versus usual care, 64% of the simulated ICERs were below a willingness to pay of $50,000 per QALY gained (Appendix 7); however, 100% of the simulated ICERs were below a willingness-to-pay of $100,000 per QALY gained. Thus, there was high certainty that, compared with usual care, both intervention strategies (CBT for psychosis delivered by physicians or nonphysicians) represented good value for money compared with usual care.

Sensitivity Analysis

We conducted 13 different scenario analyses to examine uncertainty in our parameters and structural model and their effects on the robustness of our initial results. The ICER and INB estimates for the scenarios are presented in Table 16.

The results remained robust in almost all 13 scenarios comparing CBT for psychosis by nonphysician therapists to usual care and in the majority of scenarios comparing CBT for psychosis by physicians to usual care.

For example, if the risk of relapse among patients receiving CBT for psychosis was 25% lower than the one reported in the literature[49] (Scenario 2), the ICERs of CBT for psychosis versus usual care were approximately $58,000 per QALY gained for therapy delivered by nonphysicians and approximately $105,000 per QALY gained for physicians.

Also, the ICER of CBT for psychosis by physicians versus usual care was greater than $50,000 per QALY gained if:

- The utility change associated with CBT therapy was half the value (i.e., 0.02) of the 0.04 used in the reference case analysis[91] (Scenario 4)

- Only the direct costs of CBT treatment were included: initial assessment and CBT sessions but not the downstream costs associated with treatment of schizophrenia (Scenario 9)
- Model time horizon was a lifetime instead of 5 years (Scenario 13)

In all scenarios, CBT for psychosis by physicians was dominated by CBT for psychosis by nonphysician therapists.

Table 16: Results of Sensitivity Scenario Analyses: CBT for Psychosis Strategies and Usual Care

Parameter /Assumption	CBTp by Nonphysician vs. Usual Care ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]	CBTp by Physician vs. Usual Care ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]	CBTp by Nonphysician vs. by Physician ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]
1) Delivery format for level 1 CBTp in nonphysician strategy:			
a) Reference case: 47% receive individual CBTp	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario:			
• 100% individual therapy	29,886 / INB > 0	47,196 / INB > 0	Dominated
• 100% group therapy	17,522 / INB > 0	47,196 / INB > 0	Dominated
2) Risk of relapse with CBTp:			
a) Reference case: RR = 0.65 (short-term follow-up) / RR = 0.91 (long-term follow-up)	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: 25% decrease in risk reduction	57,905 / INB < 0	105,402 / INB < 0	Dominated
3) Dropout from CBTp:			
a) Reference case: 25%	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenarios:			
• 2 × reference case probability	18,327 / INB > 0	43,402 / INB > 0	Dominated
• 0.5 × reference case probability	23,325 / INB > 0	49,563 / INB > 0	Dominated
4) Utility change associated with CBTp:			
a) Reference case: +0.04	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenarios:			
• 1.5 × reference case estimate	16,021 / INB > 0	35,137 / INB > 0	Dominated
• 0.5 × reference case estimate	33,133 / INB > 0	73,282 / INB < 0	Dominated
5) Decrease in mortality after the use of SGAs:			
a) Reference case: RR = 1	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: RR = 0.75	23,369 / INB > 0	49,739 / INB > 0	Dominated
6) Smaller risk of suicide in population with schizophrenia			
a) Reference case: RR = 27.94	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: RR = 12.86	23,331 / INB > 0	49,576 / INB > 0	Dominated

Parameter /Assumption	CBTp by Nonphysician vs. Usual Care ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]	CBTp by Physician vs. Usual Care ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]	CBTp by Nonphysician vs. by Physician ICER ($/QALY) / INB > 0 or INB < 0 ($)[a]
7) Number of sessions in level 1 CBTp (structured therapy)			
a) Reference case: 16 sessions	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenarios:			
• 8 sessions	18,132 / INB > 0	36,548 / INB > 0	Dominated
• 12 sessions	20,787 / INB > 0	43,339 / INB > 0	Dominated
8) Costs of nonphysician-provided CBTp, salary-based, FTE[b]:			
a) Reference case: $130,000/y, 30% benefits	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenarios:		No changes	
• 25% increase in salary	30,239 / INB > 0		Dominated
• $130,000/y, 17% benefits	19,035 / INB > 0		Dominated
• $110,000/y, 30% benefits	20,518 / INB > 0		Dominated
• $110,000/y, 17% benefits	16,713 / INB > 0		Dominated
9) Direct medical costs:			
a) Reference case: All costs	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: CBTp costs only	29,609 / INB > 0	55,847 / INB < 0	Dominated
10) Drug coverage:			
a) Reference case: 78%	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: 100%	22,881 / INB > 0	49,118 / INB > 0	Dominated
11) Indirect costs:			
a) Reference case: Not included	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: Included	23,485 / INB > 0	9,723 / INB > 0	Dominated
12) Discount rate:			
a) Reference case: 1.5%	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenario: 5%	23,305/ INB > 0	49, 813 / INB > 0	Dominated
13) Time horizon:			
a) Reference case: 5 years	21,520 / INB > 0	47,196 / INB > 0	Dominated
b) Scenarios:			
• 1 year[c]	28,777 / INB > 0	69,483 / INB < 0	Dominated
• 10 years	26,502 / INB > 0	50,737 / INB < 0	Dominated
• Lifetime	62,305 / INB < 0	82,627 / INB < 0	Dominated

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; FTE, full-time equivalent; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; RR, relative risk; SGA, second-generation antipsychotic medication; QALY, quality-adjusted life-year; y, year.
All costs in 2017 Canadian dollars.

[a]INB = incremental effects × $50,000/QALY − incremental costs; if INB > 0, then the strategy is cost-effective.

[b]FTE, full-time equivalent: 1,658 hours/year.

[c]All costs and effects were discounted at 1.5% in reference case and all scenarios except scenario 13 with a 1-year time horizon.

Discussion

To the best of our knowledge, this is the first study to use a decision-analytic model to examine the cost-effectiveness of CBT for psychosis provided by physicians or nonphysician therapists in adults with schizophrenia. We showed that over a 5-year time horizon and compared with usual care, CBT for psychosis provided by any certified, regulated health care provider probably represents good value for money with high certainty at various willingness-to-pay amounts. Our cost-utility analysis that ranked three strategies by increasing costs showed that, compared with usual care, CBT for psychosis by nonphysicians was associated with an ICER of $21,520 per QALY gained, while the same therapy delivered by physicians resulted in equal health benefits but was more expensive although still good value for money as well. With respect to health outcomes, we found that, over 5 years and regardless of type of provider, CBT for psychosis was associated with an increase in overall survival of 0.02 years (7.3 days), and reductions in the number of relapses (by 9%), suicides (14%), and hospitalizations (5%).

Results of our modeling study are consistent with the findings of other patient-level economic analyses alongside randomized controlled trials,[23-26,29,30] examined in our systematic review of the literature; all these analyses showed favourable cost-effectiveness for CBT for psychosis. Our modeling study has several additional strengths as it provided new insights and filled a gap in the literature regarding the long-term benefits and costs of this kind of CBT. First, we modeled the delivery of CBT for psychosis using a two-level approach with the number of sessions increasing as the illness progresses and the option of a group format when it was provided by nonphysician therapists. Second, our modeling approach enabled us to include equitable access to CBT for psychosis for all patients able to engage in therapy. Lastly, we used a longer time horizon than previous studies (i.e., 5 years) and modeled the effects of this intervention through different stages of schizophrenia, from first-episode psychosis through relapse and to treatment-resistant disease. Therefore, our results are generalizable to the majority of patients with schizophrenia in Ontario.

Limitations

Although we conducted a comprehensive economic analysis using a relatively complex individual-level Markov modelling approach, our study has several limitations.

First, we were able to model the risks of relapse and hospitalization as time-dependent variables (i.e., accounting for differences in effects over time, short-term versus long-term), but due to the limitations of the existing literature, we assumed that the efficacy of CBT for psychosis, including its associated change in health state utility, is the same for first-episode psychosis, relapsed disease, and treatment-resistant disease. However, when we modeled CBT for psychosis as less effective (Scenario 4: utility change half the size of the reference case), uncertainty increased and the ICERs for both the nonphysician and physician strategies increased but were still lower than many willingness-to-pay amounts (Table 16).

Next, supported by limited evidence, we made assumptions about the equal effectiveness of CBT for psychosis when it is provided (1) by various types of health care professionals and (2) for different numbers of sessions. Also, based on the findings of our clinical evidence review, we assumed no difference in effectiveness between group and individual formats and we did not assign any side effects to CBT for psychosis. Given differences in the costs between the two CBT strategies, future studies and guidelines may wish to specify the circumstances in which delivering CBT for psychosis by physicians would be preferable to nonphysicians; this would

help to ensure rational use of physician services and support equity of access to CBT for psychosis for adults with schizophrenia.

Finally, it is unclear how CBT for psychosis will be implemented in Ontario, and we did not include the one-time costs of training required for providers to deliver this therapy. For example, the cost of additional training for less experienced, regulated nonphysician providers is difficult to estimate; based on our expert consultations, we assumed that all training costs for less experienced therapists (who, in our model, participated in the delivery of group CBT for psychosis at level 1) were incurred through their salaries.

Conclusions

Our economic evaluation suggests that, compared with usual care, CBT for psychosis for adults with schizophrenia provided either by regulated nonphysician therapists or by psychiatrists probably represents good value for money in Ontario.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to estimate the cost burden over the next 5 years of providing access to individual or group CBT for psychosis by regulated therapists to adults diagnosed with schizophrenia. All costs are reported in 2017 Canadian dollars.[89] Reporting and analysis were done in accordance with the 2012 International Society for Pharmacoeconomics and Outcomes Research good-practice guidelines for budget impact analysis.[125]

Research Questions

- What would be the net budget impact in the first year after the adoption of publicly funding CBT for psychosis and over the following 4 years, under the assumption of a gradual uptake of this therapy in newly diagnosed adult Ontarians with schizophrenia? (Analysis 1)
- How many health care professionals (physicians and nonphysicians) would be needed to support timely access to CBT for psychosis for Ontario's population of adults with schizophrenia over the next 5 years? (Analysis 2)

Methods

Analytic Framework: Net Budget Impact (Analysis 1)

We estimated the budget impact of CBT for psychosis using the cost difference between two scenarios: current clinical practice without publicly funding CBT for psychosis (the current scenario), and the anticipated clinical practice with the publicly funded CBT for psychosis (the new scenario). Current and new scenarios were previously described in our primary economic evaluation (Table 7), where they are referred to as comparator (usual care) and intervention (CBT for psychosis). The model schematic is shown in Figure 6.

We conducted a reference case analysis and several sensitivity analyses. For all analyses, we used outputs from our cost-effectiveness model to estimate budget impact. By doing so, we ensured that our budget impact analysis accounted for heterogeneity in the patient populations with respect to age and disease severity, differences in clinical pathways, disease prognosis, and consequent differences in resource use and costs.

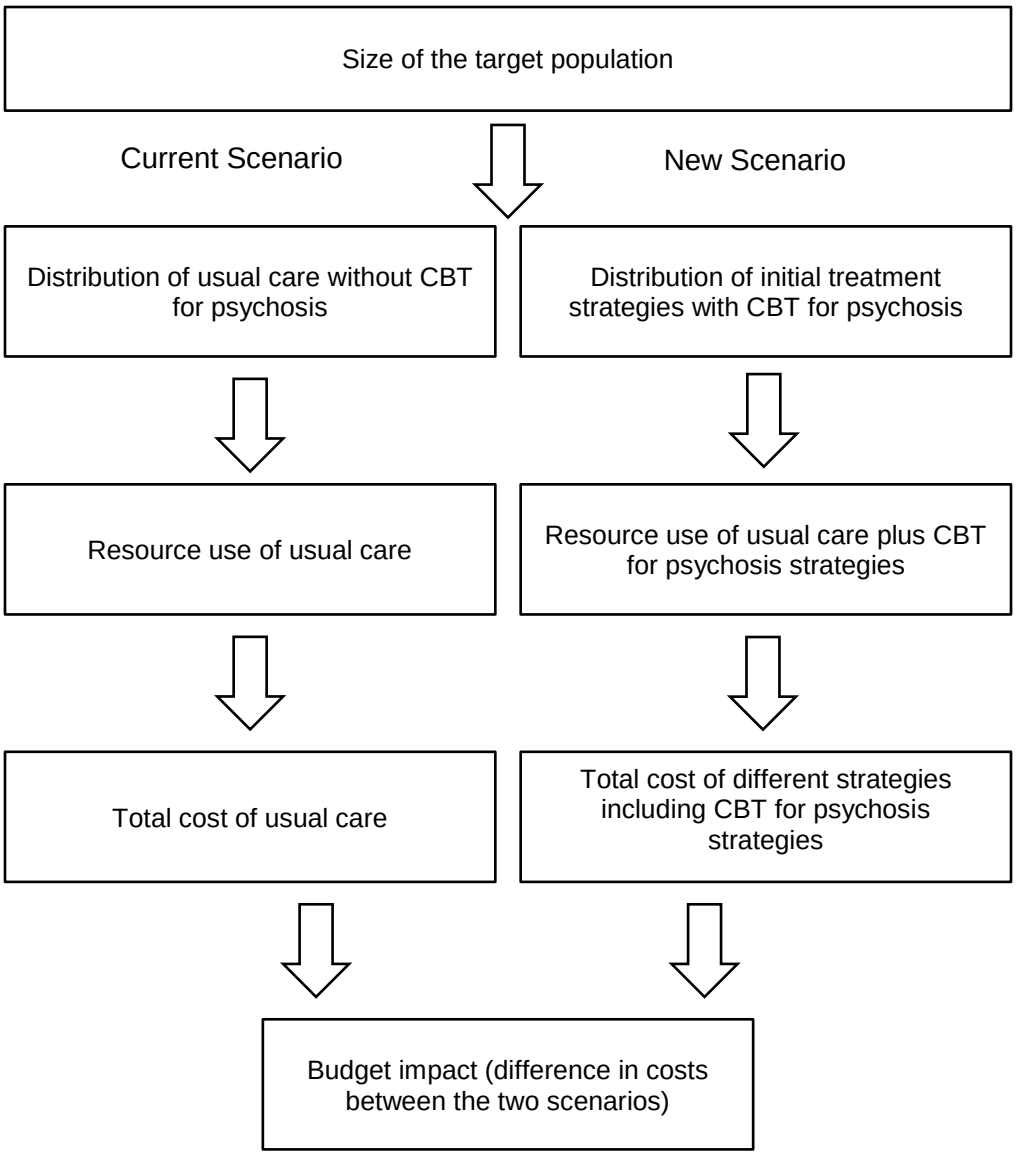

Figure 6: Budget Impact Model Schematic

Abbreviation: CBT, cognitive behavioural therapy.

Target Population

Our study population was newly diagnosed adult outpatients aged 18 years or older with a primary diagnosis of schizophrenia, eligible for CBT for psychosis. The only population considered ineligible for this therapy were patients with intellectual disabilities. Based on population-based data, the incidence of intellectual disability co-occurring in patients with schizophrenia ranges between 3.7% and 5.2%.[126]

To estimate the number of people in our target population, we applied the age- and sex-adjusted incidence of schizophrenia reported for Ontario in 2010/2011 (0.76 per 1,000 people) and assumed no growth in this rate (based on the constant incidence from 2007/2008 to

2010/2011[3]). According to census estimates, there are 11,287,810 adults aged 18 year and older in Ontario in 2017.[127] Assuming the population grows at 1% per year and 5% of people with schizophrenia are ineligible for CBT, we estimated approximately 8,150 and 8,481 people with newly diagnosed schizophrenia would be eligible for CBT for psychosis in years 1 and 5, respectively (Table 17, column 5).

Uptake

In the reference case, we assumed that access to psychotherapy would increase by 20% each year. We assumed no access to psychotherapy at baseline (0% at baseline), based on expert consultation and literature indicating that very few family health teams currently provide CBT for psychosis.[92] Adjusting for a gradual gain in access to this therapy, we estimated that the number of patients would rise from about 1,600 in year 1 (20% access) to nearly 8,500 in year 5 (100% access) (Table 17).

In separate scenario analyses, we increased the rate of uptake to 100% (full access) for all newly diagnosed patients, beginning in year 1.

Table 17: Expected Number of Patients Newly Diagnosed With Schizophrenia Eligible for CBT for Psychosis in Ontario, 2017 to 2021

Year	Estimated Number of Adults in Ontario[a]	Number of People with Schizophrenia[b]	Ineligible for CBTp,[c] N	Total Eligible for CBTp, N	Target Population, Adjusted for Increasing Rate of Uptake of CBTp,[d] N
2017	11,287,810	8,579	429	8,150	1,630
2018	11,400,688	8,665	433	8,231	3,293
2019	11,514,695	8,751	438	8,314	4,988
2020	11,629,842	8,839	442	8,397	6,717
2021	11,746,140	8,927	446	8,481	8,481

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; N, number.
[a]Assuming 1% growth in population per year (Statistics Canada).
[b]Assuming incidence of 0.76/1,000.
[c]Assuming 5% rate.[126]
[d]Assuming a 20% increase in access to CBTp each year, from 20% in year 1 to 100% in year 5.

Based on the outputs from our cost-effectiveness model, we estimated the number of patients at risk (surviving) each subsequent year after receiving either CBT for psychosis or usual care, and we adjusted the total size of our target population over the 5 years (Table 18). Similarly, dynamic cohort data were used for each scenario analysis.

Table 18: Expected Number of Patients Newly Diagnosed With Schizophrenia at Risk, by Treatment Strategy, 2017 to 2021

Year	Strategy[a]	Patients at Risk, N					Total
		Year 1	Year 2	Year 3	Year 4	Year 5	
2017	CBTp	1,630					1,630
	Usual care	1,630					1,630
2018	CBTp	3,293	1,629				4,922
	Usual care	3,293	1,629				4,922
2019	CBTp	4,988	3,291	1,629			9,908
	Usual care	4,988	3,291	1,628			9,907
2020	CBTp	6,717	4,986	3,290	1,628		16,621
	Usual care	6,717	4,986	3,289	1,627		16,619
2021	CBTp	8,481	6,715	4,985	3,288	1,626	25,095
	Usual care	8,481	6,714	4,983	3,287	1,627	25,092

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; N, number.
[a]CBT for psychosis delivered either by nonphysician therapists or by physicians.

Resources and Costs

The costs were derived from our deterministic cost-utility analysis (see Primary Economic Evaluation). As shown in Figure 6, for the new scenario and total net costs associated with it, we assumed that the costs of CBT for psychosis were added to the costs of usual care. The total cost estimates were based on the model outputs of undiscounted direct medical costs (assuming the cost of pharmacotherapy was 78% publicly funded).

Table 19 presents calculations of the average annual costs per patient from year 1 to year 5 for each strategy in the reference case analysis. These estimates were adjusted for the number of patients remaining in the model over 5 years.

Table 19: Average Costs per Patient at Risk for Each Year After Diagnosis With Schizophrenia, by Treatment Strategy

Strategy, Reference Case	Average Costs per Patient, $[a]				
	Year 1	Year 2	Year 3	Year 4	Year 5
Usual care	15,366	16,955	18,955	20,758	22,247
CBT for psychosis, nonphysician	16,695	17,191	19,176	20,982	22,523
CBT for psychosis, physician	18,491	17,466	19,492	21,301	22,836

Abbreviations: CBT, cognitive behavioural therapy.
[a]All costs in 2017 Canadian dollars. Average costs per patient were calculated using undiscounted cost outputs generated from our model simulations running for year 1 to year 5. For example, for the usual care strategy, the average unadjusted cost in year 4 was obtained by subtracting a 5-year cumulative cost estimate from a 4-year cumulative cost estimate: $94,176 − $71,971 = $22,205. After adjusting for survival, the final estimate is $22,247.
Note: CBT for psychosis by nonphysician therapists was delivered as both group and individual 16-session CBT in level 1 and as individual 24-session CBT in level 2, as described in the two-level approach modeled in our primary economic evaluation (Table 7). CBT for psychosis by physicians was delivered in the same fashion but as individual CBT only.

In summary, the dynamic cohort estimates and the corresponding cost estimates derived from our cost-effectiveness model were further used in calculating the net budget impact for the reference case and four alternative scenarios. Below, we provide details of our methods for the second analysis.

Number of Therapists Needed to Deliver CBT for Psychosis (Analysis 2)

Our second objective was to determine the number of health care professionals needed to support timely access to CBT for psychosis in Ontario. Below, we describe how we estimated the total number of people with new and relapsed schizophrenia eligible for CBT for psychosis and the resources used to provide this therapy. We conclude with an estimate of the total number of patient-hours that would be spent on the therapy over the next 5 years.

Model-Based Estimation: Number of New and Relapsed Patients Indicated for Therapy

Based on our model outputs, we first generated an average number of psychosis episodes a patient could experience in the first and following 4 years (Table 20). Any difference in the efficacy of CBT for psychosis delivered by physician versus nonphysician providers is unknown; thus, the estimates in Table 21 are the same for both strategies.

Table 20: Average Number of Psychosis Episodes per Patient for Each Year After Diagnosis With Schizophrenia

	Average Number of Psychosis Episodes				
Strategy, Reference Case	**Year 1[a]**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
CBT for psychosis, nonphysician[b]	1.095	0.193	0.191	0.185	0.176
CBT for psychosis, physician[b]	1.095	0.193	0.191	0.185	0.176

Abbreviations: CBT, cognitive behavioural therapy.
[a]New (n = 1) plus recurrent episode.
[b]Any difference in risk of relapse when CBT for psychosis is delivered by physician versus nonphysician providers is unknown.

Using these data and data from Table 18, we obtained a cohort of patients eligible for CBT for psychosis, accounting for first-episode psychosis and relapses (Table 21). These estimates yield an annual number of patients at risk and are used to estimate the number of therapists needed to deliver CBT for psychosis over the next 5 years (Tables 22 to 24).

Table 21: Expected Number of Patients at Risk, 2017 to 2021, After Adjusting for Multiple Episodes of Psychosis

		Patients at Risk, N					
Year	**Strategy**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
2017	CBTp, nonphysician	1,785					1,785
	CBTp, physician	1,785					1,785
2018	CBTp, nonphysician	3,605	315				3,920
	CBTp, physician	3,605	315				3,920
2019	CBTp, nonphysician	5,462	636	311			6,408
	CBTp, physician	5,462	636	311			6,408
2020	CBTp, nonphysician	7,355	963	628	301		9,247
	CBTp, physician	7,355	963	628	301		9,247
2021	CBTp, nonphysician	9,286	1,297	951	608	287	12,430
	CBTp, physician	9,286	1,297	951	608	287	12,430

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; N, number.

Resource Estimation

Table 22 presents our description of expected resource use (provider time) per course of CBT for psychosis, by type of provider, level of therapy (first episode or relapse), and format of therapy (individual or group). As described in our primary economic evaluation, Cost Parameters section, a full-time equivalent (FTE) therapist can be expected to conduct therapy for 1,658 hours in a calendar year.

Our calculations involve the following expert-confirmed assumptions:

- Level 1 CBT for psychosis, designed for people with newly diagnosed schizophrenia, has 16 structured sessions (meaning the structure of therapy is described in a session-by-session manual)
- If provided by nonphysician therapists, level 1 can be delivered as group therapy (1.5. hours per session) for 53% of patients,[76] in groups of 12 patients led by 2 clinicians
- Physicians delivering level 1 would do so in an individual format only, reflecting current practice in Ontario
- Level 2 CBT for psychosis has 24 sessions, conducted as individual therapy regardless of the type of the provider; this is based on the modeling approach described in our primary economic evaluation (Interventions and Comparator section)
- All analyses would be based on incident and recurrent cases of patients eligible for therapy (i.e., the number of people newly diagnosed with schizophrenia each year and their recurrent need for therapy due to relapse over the 5-year period), based on outputs from the economic model developed in our primary economic evaluation

Not knowing how CBT for psychosis will be implemented, we made the following simplifying assumptions, also confirmed by experts:

- Therapists would deliver CBT for psychosis on a full-time basis
- The costs of training less experienced therapists would be incorporated into their salaries during their year of supervised work, as part of achieving their competency for CBT for psychosis (i.e., no specific one-time training cost would be incurred)

Table 22: Resource Use for CBT for Psychosis Delivered in Two-Level Approach by Nonphysician and Physician Therapists

Strategy, Level,[a] Therapy Format	Hours per Session, N	Patients per Session, N	Proportion of Patients in Each Type of Therapy[b]	Sessions per Course of Therapy, N	Therapists, N	Resource Use per Course of Therapy, Hours[c]	FTE: Applied Hours /Year[d]
Nonphysician: Level 1, group	1.5	12	53%	16	2	48	1,658
Level 1, individual	1.0	1	47%	16	1	16	1,658
Level 2, individual	1.0	1	100%	24	1	24	1,658
Physician: Level 1, individual	1.0	1	100%	16	1	16	1,658
Level 2, individual	1.0	1	100%	24	1	24	1,658

Abbreviations: CBT, cognitive behavioural therapy; FTE, full-time equivalent; N, number.
[a] Level 1 therapy is designed for patients with first-episode psychosis; level 2 is for patients experiencing relapse or treatment-resistant schizophrenia. For more detail, see the model described in our primary economic evaluation (Table 7).
[b] Based on the Crockford and Addington, 2017.[76]
[c] Resource use related to time and human resource allocated to one course of CBT: Number of hours/per session × number of sessions per 1 course of therapy × number of therapists.
[d] Calculation of the applied hourly rate for an FTE therapist is described in our primary economic evaluation, cost parameters section.

In Table 23, we present an example of calculations to estimate the annual number of hours spent delivering CBT for psychosis (as group or individual treatment) and the number of FTE therapists needed to provide these services. This example uses data from Table 21 (Year 1) and Table 22 (information related to the delivery of CBT for psychosis).

Table 23: Calculations of Expected Patient-Hours and Number of Therapists Needed per Year to Deliver CBT for Psychosis: An Example

Strategy, Level, Therapy Format	Resource Use per Course of Therapy, Hours	Patients per Session, N	Total Expected Patients per Year, N	Proportion of Patients in Each Type of Therapy[a]	Total Expected Groups or Individuals per Year, N[b]	Total Patient-Hours per Year, N[c]	FTE Therapists per Year, N[d]
Nonphysician: Level 1, group	48	12	1,630	53%	72	3,456	2
Level 1, individual	16	1	1,630	47%	766	12,258	8
Level 2, individual	24	1	155	100%	155	3,720	2
Physician: Level 1, individual	16	1	1,785	100%	1785	28,560	17
Level 2, individual	24	1	155	100%	155	3,720	2

Abbreviations: CBT, cognitive behavioural therapy; FTE, full-time equivalent.
[b]Based on the Crockford and Addington, 2017[76] and the model described in our primary economic evaluation.
[b]Calculation of total annual number of expected groups or individuals: (total number of expected patients per year × percentage of patients splitting level 1 therapies) / number of patients per session. For example: (1,630 × 0.53) / 12 = 72 groups of patients eligible for level 1 nonphysician group therapy.
[c]Calculation of total patient hours per year spent on therapy: total number of expected groups or individuals per year × resource use. For example: 72 × 48 = 3,456 patient-hours per year.
[d]Calculation of FTE therapists needed per year: total number of patient-hours per year / 1,658. For example: 3,456 /1,658 = 2 FTE per year for level 1 group CBT for psychosis provided by nonphysicians.

Table 24 presents annual and cumulative final estimates of time (patient-hours) allocated for CBT for psychosis by nonphysician therapists and physicians over the 5-year period, given a gradual uptake of CBT therapy.

Table 24: Expected Annual Patient-Hours Spent on CBT for Psychosis, 2017 to 2021, per FTE

Year	Strategy	Number of Patient-Hours					Total Per Year
		Year 1	Year 2	Year 3	Year 4	Year 5	
2017	CBTp, nonphysician	19,433					19,433
	CBTp, physician	32,280					32,280
2018	CBTp, nonphysician	39,241	7,553				46,794
	CBTp, physician	65,181	7,553				72,734
2019	CBTp, nonphysician	59,449	15,264	7,459			82,172
	CBTp, physician	98,750	15,264	7,459			121,473
2020	CBTp, nonphysician	80,068	23,117	15,064	7,229		125,478
	CBTp, physician	132,992	23,117	15,064	7,229		178,402
2021	CBTp, nonphysician	101,074	31,134	22,825	14,601	6,894	176,528
	CBTp, physician	167,891	31,134	22,825	14,601	6,894	243,345

Abbreviation: CBTp, cognitive behavioural therapy for psychosis; FTE, full-time equivalent.

Analysis

To address different scenarios in Ontario, we conducted the following budgetary impact analyses:

- **Reference case analysis –** to estimate the net budget impact of two CBT for psychosis strategies compared with usual care, using the two-level approach described in our cost-effectiveness model (see Table 7):
  - CBT for psychosis delivered by nonphysician therapists in both group and individual formats for 16 sessions in level 1, and as individual therapy for 24 sessions in level 2
  - CBT for psychosis delivered by physicians in the same fashion but as individual therapy only
- **Sensitivity analysis, scenario 1 –** to estimate the net budget impact if the number of CBT sessions in level 1 was smaller (8 or 12 sessions vs. 16)
- **Sensitivity analysis, scenario 2 –** to estimate the net budget impact if CBT for psychosis was provided only as group therapy by nonphysician therapists
- **Sensitivity analysis, scenario 3 –** to estimate the net budget impact of time-limited CBT for psychosis (level 1 only)
- **Sensitivity analysis, scenario 4 –** to estimate the net budget impact of CBT for psychosis considering only the costs of CBT therapy

Results

Analysis 1: Net Budget Impact, Reference Case

In Table 25, we present calculations of the 5-year net budget impact in detail, using data from Table 18 and Table 19. We calculated the total budgets for the current scenario (usual care) and for the new scenario of adding CBT for psychosis to usual care, with the psychotherapy delivered by nonphysician therapists.

Adopting CBT for psychosis by nonphysician therapists would lead to an increase in costs of about $2.2 million in year 1, assuming the therapy was provided to 20% of eligible patients that year. Assuming full access is achieved by year 5 (100% of eligible patients), the cumulative increase in costs would be about $15.2 million (i.e., total 5-year net budget impact). These results suggest that, once all newly diagnosed, eligible patients have access to CBT for psychosis, this strategy would result in extra spending of approximately $3 million per year, on average, compared to current usual care.

Table 25: Five-Year Net Budget Impact of Adopting CBT for Psychosis Provided by Nonphysician Therapists in Ontario

	Total Budget Impact, $					
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Totals**
CBTp, nonphysician	27,212,881					27,212,881
Usual care	25,046,378					25,046,378
Net budget impact	**2,166,503**					**2,166,503**
CBTp, nonphysician	54,970,020	28,004,411				82,974,431
Usual care	50,593,684	27,620,123				78,213,808
Net budget impact	**4,376,335**	**384,288**				**4,760,623**
CBTp, nonphysician	83,279,580	56,576,131	31,237,979			171,093,689
Usual care	76,649,432	55,799,770	30,858,818			163,308,021
Net budget impact	**6,630,148**	**776,360**	**379,161**			**7,785,669**
CBTp, nonphysician	112,149,834	85,715,159	63,089,595	34,159,438		295,114,026
Usual care	103,221,235	84,538,941	62,343,153	33,773,740		283,877,069
Net budget impact	**8,928,599**	**1,176,218**	**746,442**	**385,699**		**11,236,957**
CBTp, nonphysician	141,589,166	115,438,686	95,593,201	68,990,315	36,622,067	458,233,435
Usual care	130,316,809	113,837,635	94,453,005	68,232,503	36,196,257	443,036,210
Net budget impact	**11,272,357**	**1,601,051**	**1,140,196**	**757,812**	**425,809**	**15,197,225**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis.
Note: Net budget impact = budget impact for a CBT strategy − budget impact for usual care.

In contrast, if CBT for psychosis were delivered entirely by physicians, the net budget impact would range from $5.1 million in year 1 to $35.4 million in year 5 (Table 26). On average, the province would need to spend an extra $7 million per year to adopt this CBT strategy, once full uptake was achieved.

Table 26: Five-Year Net Budget Impact of Adopting CBT for Psychosis Provided by Physicians in Ontario

	Total Budget Impact, $				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
CBTp, physician	30,139,982	89,334,515	181,470,082	310,105,446	478,439,982
Usual care	25,046,378	78,213,808	163,308,021	283,877,069	443,036,210
Net budget impact	**5,093,603**	**11,120,707**	**18,162,062**	**26,228,378**	**35,403,773**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis.

Budget Impact Scenario 1: Fewer Sessions in Level 1 CBT for Psychosis

Table 27 and Table 28 show the net budget impact of adopting CBT for psychosis if level 1 therapy (i.e., for newly diagnosed patients) were delivered in 8 or 12 structured sessions, instead of 16 sessions as in our reference case. As expected, overall net budget impact decreased as the number of sessions decreased. As shown in Table 27, the 5-year net budget impact in the 8-session scenario, compared to usual care, would be $11.1 million for CBT for psychosis delivered by nonphysician therapists and $25.7 million if delivered by physicians.

Comparing the 8-session and reference case (16-session) scenarios (Table 27 vs. Tables 25 and 26), the decrease in net budget impact ranged from 17% to 36% if nonphysician therapists delivered the sessions, and from 20% to 42% for physicians, depending on the rate of access and duration of follow-up across the 5-year period. For example, compared to the reference case, the year 1 net budget impact of the briefer therapy was 36% ($0.77 million) lower if provided by nonphysicians and 42% ($2.14 million) lower if provided by physicians. Correspondingly, the total 5-year net budget impact decreased by 27% ($4.09 million) for nonphysician therapists and by 28% ($9.75 million) for physicians, compared with the reference case estimates.

Table 27: Scenario 1, Eight Sessions of Structured CBT for Psychosis: Five-Year Net Budget Impact

	Total Budget Impact, $				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Usual care	25,107,651	78,276,586	163,507,255	284,220,384	443,449,209
CBT for psychosis, nonphysician	26,500,670	82,246,972	169,456,046	292,487,379	454,555,935
CBT for psychosis, physician	28,061,419	87,213,051	177,040,664	303,264,847	469,100,351
NBI, CBTp by nonphysician vs. usual care	**1,393,019**	**3,970,386**	**5,948,791**	**8,266,995**	**11,106,725**
NBI, CBTp by physician vs. usual care	**2,953,768**	**8,936,465**	**13,533,410**	**19,044,463**	**25,651,142**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; NBI, net budget impact.
Note: Net budget impact = budget impact for a CBT strategy – budget impact for usual care.

Slightly smaller decreases in net budget impact were seen in the 12-session scenario (Table 28 vs. Tables 25 and 26). The decrease in net budget impact, compared to the reference case, ranged from 8% to 19% for CBT for psychosis by nonphysician therapists, and from 10% to 21% for CBT for psychosis by physicians, depending on the rate of access and duration of follow-up over the 5 years.

As shown in Table 29, the 5-year net budget impact in the scenario with 12 sessions was $12.36 million for CBT for psychosis by nonphysician therapists and $30.24 million for CBT for psychosis by physicians. These totals are 19% ($2.84 million) lower for nonphysician therapists and 15% ($5.17 million) lower for physicians, compared with the corresponding reference case estimates.

Table 28: Scenario 1, 12 Sessions of Structured CBT for Psychosis: Five-Year Net Budget Impact

	Total Budget Impact, $				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Usual care	25,080,901	78,247,643	163,478,236	284,231,476	443,558,444
CBT for psychosis, nonphysician	26,865,949	82,619,073	170,302,601	293,823,773	455,915,285
CBT for psychosis, physician	29,120,213	88,292,674	179,302,513	306,738,398	473,794,961
NBI, CBTp by nonphysician vs. usual care	**1,785,048**	**4,371,430**	**6,824,364**	**9,592,297**	**12,356,841**
NBI, CBTp by physician vs. usual care	**4,039,312**	**10,045,031**	**15,824,277**	**22,506,922**	**30,236,517**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; NBI, net budget impact.
Note: Net budget impact = budget impact for a CBT strategy – budget impact for usual care.

Budget Impact Scenario 2: Group Format for All, CBT for Psychosis by Nonphysician Therapists

As shown in Table 29, there would be a large decrease in the net budget impact of CBT for psychosis by nonphysician therapists if all patients received group therapy as their initial treatment (level 1 CBT). The net budget impact of this scenario ranged from $1.10 million in year 1 (with an uptake of 20%) to $9.65 million in year 5 (100% uptake). Compared to the corresponding estimates in the reference case (Table 25) in which close to half the patients received individual therapy, the net budget impact decreased between 37% (5-year cost burden) and 49% (1-year cost burden).

Table 29: Scenario 2 – Group Format for All, CBT for Psychosis by Nonphysician Therapists: Five-Year Net Budget Impact

	Total Budget Impact, $				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
CBT for psychosis, nonphysician	26,146,316	80,819,969	167,829,680	290,718,494	452,684,076
Usual care	25,046,378	78,213,808	163,308,021	283,877,069	443,036,210
Net budget impact	**1,099,938**	**2,606,162**	**4,521,660**	**6,841,425**	**9,647,866**

Abbreviations: CBT, cognitive behavioural therapy.

Budget Impact Scenario 3: Time-Limited CBT for Psychosis (Providing Level 1 Only)

Table 30 shows the budget impact of offering only the level 1 CBT for psychosis (16 sessions), excluding the follow-up therapy for patients who experience relapse. As in all our scenarios, we assumed the uptake of CBT for psychosis would increase at 20% per year with full access achieved in year 5. The net budget impact of time-limited therapy by nonphysician therapists ranged from $1.60 million in year 1 to $3.63 million in year 5, compared to usual care. For therapy delivered by physicians, the net budget impact for time-limited CBT for psychosis compared to usual care ranged from $4.21 million in year 1 to $17.17 million in year 5.

Providing time-limited CBT for psychosis in 16 structured sessions is a less costly option for the following reasons:

- It is associated with large decreases in net budget impact for both CBT strategies (delivery either by physicians or nonphysicians) compared to the reference case estimates
- There are large cost-savings in the net budget impact from year 2 to year 5, due to reduction of downstream treatment costs

Compared with the corresponding estimates in the reference case, the net budget impact of time-limited CBT for psychosis by nonphysician therapists was 26% lower in year 1 and 76% lower after 5 years. If time-limited CBT for psychosis was provided by physicians, the difference in net budget impact decreased from 17% in year 1 to 51% over 5 years.

Table 30: Scenario 3 – Time-Limited CBT for Psychosis: Five-Year Net Budget Impact

Strategy	Total Budget Impact, $				
	Year 1	Year 2	Year 3	Year 4	Year 5
Usual care	25,046,378	78,213,808	163,308,021	283,877,069	443,036,210
CBT for psychosis, nonphysician	26,650,771	81,061,783	166,908,888	287,710,088	446,662,369
CBT for psychosis, physician	29,254,326	86,320,965	174,876,549	298,439,871	460,208,720
NBI, CBTp by nonphysician vs. usual care	**1,604,392**	**2,847,975**	**3,600,868**	**3,833,019**	**3,626,159**
NBI, CBTp by physician vs. usual care	**4,207,948**	**8,107,157**	**11,568,528**	**14,562,802**	**17,172,511**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; NBI, net budget impact.
Note: Net budget impact = budget impact for a CBT strategy – budget impact for usual care.

Budget Impact Scenario 4: Only the Costs Associated With CBT for Psychosis

Table 31 presents the net budget impact considering only the costs of initial assessment and CBT sessions and no additional costs associated with usual care. As a result, the estimates were slightly higher than those of the reference case, which assumed that CBT for psychosis would always be delivered in conjunction with usual care.

When accounting only for the psychotherapy costs, the net budget impact of CBT for psychosis by nonphysician therapists ranged from $2.22 million in year 1 (uptake of 20%) to $20.21 million in year 5 (full uptake), compared to usual care. For therapy delivered physicians, the net budget impact ranged from $5.24 million in year 1 to $40.85 million in year 5.

Table 31: Scenario 4 – Only Costs Associated With CBT Therapy: Five-Year Net Budget Impact

Strategy	Total Budget Impact, $				
	Year 1	Year 2	Year 3	Year 4	Year 5
NBI, CBTp by nonphysician vs. usual care	2,224,265	5,267,458	9,265,738	14,245,231	20,207,772
NBI, CBTp by physician vs. usual care	5,236,253	11,797,436	19,898,600	29,581,433	40,849,362

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; NBI, net budget impact.

Analysis 2: Estimating the Number of Therapists Needed in Ontario, 2017 to 2021

Based on the expected patient-hours spent on CBT for psychosis if this treatment were increasingly available over the next 5 years (Table 23), we estimated that 110 regulated nonphysician cognitive behavioural therapists or 150 physicians trained in CBT for psychosis will be needed by 2021 to provide CBT for psychosis in the management of schizophrenia among adults in Ontario (Table 32).

Table 32: Expected Number of Therapists Needed to Provide CBT for Psychosis in Ontario, 2017 to 2021

Year	Strategy	Therapists Needed, N					Total Therapists Per Year, N
		Year 1	Year 2	Year 3	Year 4	Year 5	
2017	CBTp, nonphysician	12					**12**
	CBTp, physician	19					**19**
2018	CBTp, nonphysician	24	4				**28**
	CBTp, physician	40	4				**44**
2019	CBTp, nonphysician	36	9	4			**49**
	CBTp, physician	60	9	4			**73**
2020	CBTp, nonphysician	48	14	9	4		**75**
	CBTp, physician	80	14	9	4		**107**
2021	CBTp, nonphysician	61	19	14	9	4	**107**
	CBTp, physician	101	19	14	9	4	**147**

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; N, number.

Discussion

We conducted a model-based budget impact analysis to estimate the range of investment needed to enable full access to CBT for psychosis for adults with schizophrenia in Ontario. Our two-level model takes equity issues into account because it offers individual in-person CBT for psychosis as the first option for a subset of patients with schizophrenia who may not do well in group therapy.

After accounting for a 20% increase in access per year (from 0% at baseline to 100% in year 5), the total 5-year net budget impact of publicly funding CBT for psychosis for the management of schizophrenia in Ontario adults was estimated to be about $15.2 million, if the psychotherapy is provided by certified, regulated nonphysician therapists. On average over the next 5 years, the province would need to spend an extra $3 million yearly to gradually increase access to this therapy by regulated nonphysician therapists.

If CBT for psychosis is provided by physicians (e.g., psychiatrists), the net 5-year budget impact would be higher: about $35.4 million, or $7 million yearly on average, again assuming uptake increased by 20% each year.

Our analysis indicates that the 5-year cost burden of adding CBT for psychosis to usual care would be smaller if the level 1 CBT for psychosis (i.e., initial treatment for newly diagnosed patients) were provided as a group therapy to everyone, through 8 to 12 sessions instead of 16, or as a course of time-limited therapy.

Finally, we forecasted that over the next 5 years approximately 110 certified, regulated nonphysician therapists or 150 physicians trained in CBT for psychosis will be needed to provide CBT for psychosis for a total of 12,430 patients in Ontario. It is important to recognize that any regulated health professional providing CBT for psychosis should be trained and experienced in delivery of this type of CBT for patients with schizophrenia and should be certified by the national credentialing body to ensure quality of therapeutic delivery.

Furthermore, implementation of CBT for psychosis might be facilitated if incorporated into existing mental health programs.

Limitations

Our analyses are restricted by our modeling assumptions, and therefore, our estimate of the net budget impact is possibly underestimated. Our model takes into account the whole course of schizophrenia starting from incident (newly diagnosed) psychosis and following through relapsed and treatment-resistant disease over the course of 5 years. One could instead approach the budget impact calculations by multiplying all prevalent cases in Ontario (i.e., everyone with schizophrenia, rather than newly diagnosed people only) with the yearly direct medical costs estimated from our model. We did not take this approach because it could wrongly equate the costs of treating prevalent cases (patients with prior psychotic episodes) and incident cases (patients with first-episode psychosis).

In addition, our estimate of the 5-year net budget impact may be imprecise because we do not know how CBT for psychosis will be implemented. Therefore, we did not separately cost the one-time training in CBT for psychosis for less experienced, regulated nonphysician therapists who were assumed to participate in the delivery of group CBT for psychosis. Instead, we assumed that this training cost would be incurred through their salaries. We also assumed that the therapy would be delivered by full-time therapists treating incident cases of schizophrenia and all relapsed episodes over 5 years; still, the number of therapists needed for the whole population of Ontario patients with schizophrenia may be underestimated.

Conclusions

We found that publicly funding CBT for psychosis in addition to usual care in the management of schizophrenia in Ontario adults would have a total net budget impact of about $15 million over the next 5 years if provided by regulated nonphysician therapists, or about $35 million if provided by physicians. Costs will vary depending on the type of provider, format of therapy, and rate of access. We assumed access to CBT for psychosis would increase by 20% per year to reach 100% access by 2021. Approximately 110 nonphysician therapists or 150 physicians (full-time equivalents) trained in CBT for psychosis would be needed to provide this psychotherapy to more than 12,000 patients with schizophrenia over the 5-year period.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, and preferences of people in Ontario who have lived experience with psychosis due to schizophrenia. The treatment focus was cognitive behavioural therapy (CBT) versus medication or no treatment.

Background

Patient, caregiver, and public engagement provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the patient, the patient's family and other caregivers, and the patient's personal environment. It also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., sometimes typical outcome measures do not reflect what is important to those with lived experience).[128-130] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, priorities, preferences, and values of those with lived experience in Ontario are important to understand and consider, we contact and speak directly with people who live with a given health condition, including those who may have experience with the intervention we are exploring.

Mental health conditions are prevalent in Canada and Ontario and can have a significant impact on patients and their families and on their quality of life. Approximately 11.5 per 1,000 people aged 18 to 64 years in Ontario have been diagnosed with schizophrenia, and they are at an increased risk of having other psychiatric conditions including substance use disorders, depression, anxiety, and experiencing homelessness and unemployment.[1,3] For this health technology assessment, we spoke with patients and family members who have lived experience with psychosis due to schizophrenia. All those interviewed had experience with various treatment options used to manage psychotic episodes and schizophrenia in general. Gaining an understanding of people's day-to-day experience of dealing with schizophrenia, including their experience with cognitive behavioural therapy for psychosis, helps us assess the potential value of this treatment from the perspective of patients and families.

Methods

Engagement Plan

The engagement plan for this health technology assessment focused on consultation to examine the experiences of patients with schizophrenia and those of their families and other caregivers, including their experience with cognitive behavioural therapy. We engaged participants through phone interviews.

Primarily, we used qualitative interviews because this method of engagement allows us to explore the meaning of central themes in the experiences of patients with schizophrenia, as well as those of their families and caregivers. Our main task in interviewing is to understand what

people tell us and gain an understanding of the story behind their experiences.[131] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our primary choice of an interview methodology.

Participant Outreach Process

We actively reached out to patients, families, and caregivers with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, health clinics, and schizophrenia support associations to spread the word about this engagement activity and to make contact with patients, families, and caregivers, including those with experience with CBT for psychosis associated with schizophrenia.

Inclusion Criteria

We sought to speak with patients who had experienced treatment with psychotherapy, specifically cognitive behavioural therapy for psychosis associated with schizophrenia. Patients were not required to be currently receiving psychotherapy treatment, only to have had lived experience with it. We sought a broad geographic, cultural, and socioeconomic representation to elicit possible equity issues in accessing and receiving psychotherapy treatment.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

We conducted interviews with 13 people. We spoke with 7 participants with schizophrenia, who may or may not have had direct experience with CBT. We also spoke with 6 parents of adults with schizophrenia who were able to speak of the role of caregivers and families in the care of a patient with schizophrenia and in accessing CBT in Ontario. Participants were all over 18 years of age and were recruited from several locations in Ontario, both rural and urban.

Approach

At the beginning of the interview and focus groups, we explained the role of Health Quality Ontario, the purpose of the health technology assessment, the risks of participation, and how personal health information would be protected. We gave this information to participants both verbally and in a printed letter of information (Appendix 8). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded interviews and then had the recordings transcribed.

Interviews lasted 20 to 90 minutes. They were loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[132] Questions focused on the impact of schizophrenia on patients' and families' quality of life, their experiences with treatment options, their perceptions of the benefits or limitations of CBT, and their ability to access this treatment in Ontario. See Appendix 9 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information across participants. This method consisted of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[133,134] We used the qualitative data analysis software program NVivo (QSR International, Doncaster, Victoria, Australia) to identify and interpret patterns in the interviews. The patterns we identified then allowed us to highlight the impact of health conditions and treatments on the patients, family members, and caregivers we interviewed.

Results

Lived Experience of Schizophrenia and Psychosis

Patients and families interviewed reported on the unique nature of the challenges and struggles with schizophrenia and psychosis. Their lived experience with mental health issues were distinctive and personal, and the symptoms and manifestations of psychosis associated with schizophrenia were varied. Despite the unique nature of their conditions, however, patients and families were able to report on some commonalities. These included the negative and burdensome impact schizophrenia could have on family members and caregivers, as well as the challenging nature of this disease which often resisted diagnosis for years.

Diagnosis

The diagnosis of schizophrenia often came several years after symptoms first developed. Both patients and family members reported that the diagnosis was a challenge to obtain, as often the symptoms were attributed to social or personality traits of the patient. These symptomatic traits would lead the patient to withdraw from social situations with friends or family members and resist any suggestion of illness. The complex nature of schizophrenia and its potential for delusional behaviour only exacerbated this situation. In interviews, some patients and family members reported that this avoidance of diagnosis or acknowledgment of mental health challenges could last for years.

> *I think I started developing symptoms when I was probably about 19 or 20, and I was diagnosed when I was 23.*
>
> *Well, I denied that anything was wrong with me, so that's why I was homeless for so long and I refused psychiatric treatment*.
>
> *Well, it's really scary, because all the delusions and all the voices are telling you that it's completely real, and it's really hard to get help if you have schizophrenia because a lot of the times you don't identify with your behaviour. And you think everybody else is kind of crazy, except for yourself.*

For some patients, it was only a dramatic episode of psychosis or other mental instability that led to admission to a hospital and the ultimate diagnosis of schizophrenia. This episode could involve the medical system or the justice system. Several parents interviewed reported that they had lost contact with their child, and it wasn't until their mental health challenges became overwhelming that the child reached out and they learned of the diagnosis of schizophrenia.

> *I said, "There's something wrong with me. I don't know what's wrong with me, but I know I need help." But it's very hard to get to that point, and you know, a lot of people don't ask for help …*
>
> *He was out on the sidewalk, outside of his apartment, banging his head on the sidewalk. And they knew there was something dramatically wrong with him, so they took him to the local hospital.*
>
> *It took us three to four weeks searching from Halifax to Toronto to find him and by this time he was in jail, in solitary confinement, and he was totally psychotic. He'd had a complete psychotic break.*

Impact of Schizophrenia

As mentioned, patients and families reported on the enormous impact that schizophrenia and psychosis could have on their daily lives. This was especially true prior to getting a diagnosis and potentially obtaining effective treatment. For patients with poorly controlled schizophrenia, the disease was often associated with social or personality changes, leading to social isolation and occasionally risky behaviour. In particular, patients' delusions could cause unusual and inconsistent behaviour, leading to extreme challenges in their ability to function in regular activities and social situations.

> *Sometimes I'd be up all the time, or sometimes I just couldn't get out of bed.*
>
> *Basically, the delusions and everything occupy your time completely, like, it basically enables [disables] you from functioning or even participating in society.*
>
> *I mean, as far as mental illness goes along with the schizophrenia, anxiety, severe anxiety and depression, they're also factors.*

However, a number of those interviewed emphasized that the condition cannot be cured and that even well-controlled schizophrenia can be a daily burden.

> *Well, having schizophrenia, in my opinion, is a daily struggle, because you're always struggling to manage your health. It's not like, you see people who don't have schizophrenia, they do not think in terms of coping mechanisms, they do not think from situation to situation how will I cope with this, whereas someone like me does.*

Social Impact

Patients and families reported that in the early stages of schizophrenia, prior to treatment or even diagnosis, it often negatively impacted multiple areas of a patient's social life. For patients who were in school, they could struggle academically or even withdraw from the education system entirely.

> *Well, the problem is, it's not good for my family, but also for my academics. The quality of my work really started to suffer. I mean, the work was not very good, so definitely something needed to be done because they wanted me to finish by the end of the year.*

If the patient was a little older when the symptoms first manifested, it could affect their ability to hold employment. The behavioural symptoms of schizophrenia led to termination or the inability to retain interest in work. For those able to continue working, the jobs were reported to be of low value and responsibility.

> *It's not—it's work they gave me but it's not—I can go at my own pace, I don't have—and if I don't show up, it's no big deal. It's not a real job.*
>
> *So then after that, I lost my job—it seems to be the story of my life.*
>
> *But then his marriage fell apart and he started to drink and not show up for work. Well, he lost his job, of course. And that was the beginning of a really difficult period for him. And as I was saying, it was difficult for us, but [our son who has schizophrenia] will tell you, the person who was ill is really suffering.*
>
> *Well, in 2006 the delusions started interfering with my ability to work and by the time—and I had to go on long-term disability—and by the time 2008 came along, well 2007 I guess, it interfered with my ability to parent my children and then in 2008 it interfered with my ability to pay my bills and pay my rent, so I was about to be evicted from my home and then I was homeless for three years. It had a drastic effect on my life, yeah.*

A number of patients also reported withdrawing from social situations and from interactions with friends and loved ones. Several parents reported losing contact with their child for weeks and months at a time and worrying about their welfare.

> *[Schizophrenia] interrupts their lives. They lose their friends because they're in a very different place and friends have a hard time relating to them.*
>
> *As far as the social aspect, friends deserted [him]. Family, those who understood, stayed.*
>
> *… So he was like 26 and friends were so worried about him, they took him to the hospital, were extremely worried … so he was hospitalized, admitted for almost a month.*

Emotional Impact

Participants reported that their experience with schizophrenia was often associated with stigma and shame. Patients and families felt that the disease was not well understood by those around them. Patients reported avoiding social situations, knowing the stigma they may potentially face. This included withdrawing from those around them, including family members, out of mistrust and fear of rejection. Family members also reported feeling stigmatized and judged based on the mental health challenges of their loved one.

> *I have done it on many occasions, there's a way to remove the fear that, remove the shame that comes with having schizophrenia, and feel more at ease, accepting of yourself. I don't think people should hide their illness, nobody should have to hide their illness. It's an illness.*

> *Our family suffered through the stigmatization that goes along with the diagnosis. And strangely enough, even to this day I find stigma is generated quite a bit from the health professionals themselves in treating families; there is an automatic scepticism about family members.*

> *So, you know, there's just a lot of ignorant people and including, I hate to say it, but including my partner, that don't know how to deal with people that do have severe mental illness, and I feel it is partly education and not, you know, people not being educated and understanding the illness.*

Parents and families from more rural locations commented that the nature of smaller communities could exacerbate this situation and cause increased stigma and shame.

> *But sometimes in small communities, there's the—whole confidentiality in small communities can be really hard to overcome, because everybody knows everybody. That's one of the struggles that small communities have, because everybody knows that Jane is acting funny down the street, you know, because everybody sees it and everybody knows everybody.*

For parents and family members, this was an emotionally challenging situation, seeing their child behave in unconventional ways and potentially resist help. Parents often spoke of the frustration of trying to secure treatment for their child, only to have their child resist or refuse it or even acknowledge that anything was wrong. In addition, the challenges surrounding mental illness could affect other members of the family as well; several parents spoke of how the challenges and time commitment to their child with schizophrenia adversely affected their other children.

> *I guess, just trying to, you know, help him with it and, you know, try to, like just being, he's my son, so just even seeing him in a state like that is very hard. Like it's something that you, I wouldn't wish it on my worst enemy, because the illness is a really terrible illness.*

> *And really, all of our attempts to try to get any help, any kind of professional help, was thwarted by his insistence that there was nothing wrong with him, that he was okay, that he didn't like his school and his friends were against him. His whole demeanour started to change, he stopped taking care of himself and he was looking grubby.*

> *To describe in a nutshell how my husband and I felt after these episodes or if we've gone to see him let's say during the week or there was a crisis and he called us, we felt like the next day emotionally like we'd actually been run over by a truck. We just felt awful. It's hard to describe it, we just felt like really sick, like we had a really bad cold but we weren't sick physically. It just affects you so much.*

> *You know, it was very, very difficult and it was difficult for his brothers and his sister as well, because all of a sudden all of our focus was on him. We didn't have a lot of time for our other children.*

Treatment for Schizophrenia

Patients reported pharmacotherapy as the primary treatment available to help treat their schizophrenia and related psychosis. Patients reported great familiarity with the different types of pharmacotherapy and the variety of medication options available. Occasionally, it would take time to find a medication that was most effective and did not have side effects. This process could become a barrier to effective treatment if a patient was not motivated or fully accepting of the need for medications.

> *A lot of the times when I was first introduced to medication, I stopped for a long time. And there's side effects to the medication, like lack of motivation, that are really hard to come over, and come – you have to kind of push yourself even, and do things, whether you want to or not, you know*

> *They told me they wanted me to take the medicine, but they didn't do anything to make me do it, so I stopped taking the medicine.*

> *I really liked the different educations around the medications, because sometimes people can find – you know, or learn about something else that works better.*

However, the majority of those interviewed said that one of the largest challenges with medication was the patient's initial resistance to this treatment. An unwillingness to accept the diagnosis of schizophrenia and psychosis and the need for medication was seen as a major barrier to successful treatment.

> *For our son, the medication is the key thing. He would never have taken medication but because he was mandated to do so—of course it's like a Catch 22 situation—the person doesn't believe they're ill, could be suffering from paranoia in many aspects of their illness where they don't want to comply, they don't understand, they can't and they don't comply because they're so ill. But … once they start taking the medication, then they have—the person can have more insight and then start to understand why they need their medication.*

> *I mean I refused medication for many years and I lost everything in my life, so I feel that now it's at an adequate dose that it's actually helping me and there are minimal side effects.*

Once this acceptance occurred, treatment was often relatively effective and beneficial to both patients and their families. Parents reported feeling that antipsychotic medication could help return their relationship with their child back to "normal."

> *When I was introduced to medication and started trying to identify with my behaviour, you know, there was a great sense of relief.*

> *I've been on all types of stuff so I know what medicines can do. So, we all have different stuff but the stuff I'm on now is what [the doctor] prescribed and it's worked, they're pretty good. It's got my thoughts to where I know that things are fictional and I know the differences between reality and I can stay settled because I know these things aren't happening, where no other medicine has done that before.*

> *It cleared up the psychosis. He began to become himself again. He came home one weekend and he looked at me and he said, "Oh my God, Mom, this must have been really horrendous for you." And suddenly I had my son back. He actually had some insight. Yes, so it did. It cleared up his thinking. It unscrambled his thinking completely.*

Patients and families also reported on the particular potential benefits of antipsychotic medication and how it could help patients become more willing to accept other treatment, including psychotherapy such as CBT for pyschosis.

> *When I was in psychosis, the number one thing is medication; without medication you never, I mean it's the foundation, you need antipsychotic medication; you need the proper medication to get better. So yeah, for psychosis the number one [treatment] is medication, without a doubt; CBT comes later when you're a bit more stable. Without medication, someone with schizophrenia can never really live a proper life; that's why I wonder about some of those people who go on and off their medications.*

> *He's moved through medication adjustments. You know, for the first year I could just see him getting better and better and better, and he lived with us when he came out of the hospital.*

> *No. It was offered to me, but I was so convinced that my delusions were real that I didn't think anybody could convince me of a different way of thinking, you know, about them. So basically, I refused cognitive behavioural therapy that was being offered to me.*

Cognitive Behavioral Therapy for Psychosis

Access to CBT for Psychosis

Along with the challenges associated with trying to help someone with schizophrenia who does not agree to or acknowledge the need for treatment, patients and their families encountered challenges in accessing effective psychotherapy. Often the barrier to access was simply capacity; wait times were too lengthy or there were not enough services available. Patients and families who lived in rural areas felt at times that they would need to move to a location with more services.

> *Once you get in, you get help, but it's difficult to get in because there's so much pressure on the system. There are people lined up in London, you know, they are always at least 6 to 12 people in the emergency waiting for a mental health bed.*

> *There are not enough psychiatrists. To get a psychiatrist with CBT is rare. Some psychiatrists don't do CBT but talk to patients.*

> *I know myself, if I started struggling and getting really sick again, I'd probably go to Toronto, or … that's what I've done in the past is, I've gone to Toronto to get help.*

> *That's the type of help he was getting and it was so minimal, and so I thought okay maybe if we move to a bigger city, a bigger area, there'd be more resources.*

Many patients and parents expressed extreme frustration and desperation at trying to access effective and affordable care for their mental health condition.

> *Well, the biggest challenge was getting my son the help he needed. That's like absolutely huge. It's seems—it's just, it's an ongoing nightmare is the way I would say it to myself. It's an ongoing nightmare for us as parents or family members to see our loved one suffering so much. Ongoing nightmares because it just spirals down into the person becoming more unwell, making poor decisions, being in unsafe conditions, constant stress for us.*

> *Well, it just seems like as far as like even waitlists and programs not running and distance, there's always something that seems to come up that nothing transpires, nothing comes of it. It's like, you know, I try and find out, I contacted so many people trying to get information and trying to get him into programs and things, and nothing ever comes of it.*

In addition, for services not publicly funded, the significant cost associated with therapy could be prohibitive for some families.

> *Again, I think the major one for us, given the dramatic situation we had, it was we couldn't access things either because of affordability, or the support that we were looking for was not covered under any government program that we even then could not afford ourselves.*

Impact of CBT for Psychosis

A number of patients and families reported feeling that the success of CBT was partially dependent on the ability of the patient to use it. This is a similar sentiment to that expressed about other treatment options for schizophrenia and psychosis: if a patient is resistant to treatment or does not acknowledge their mental health condition, treatment will not be effective.

> *When someone is really ill … CBT does not work. Someone has to be reasonably under control before they get CBT. In the early throws of psychosis, people may not benefit. In the early stages, people are in denial … so they will not sit with a psychiatrist to hear about coping mechanisms when they don't even agree that they have psychosis.*

However, cognitive behavioural therapy was felt to be quite effective for those patients who were able to access and willing to use it. Patients and families spoke of the tools and skills that CBT provided for patients to identify and address their own thoughts and behaviours.

> *He never acknowledges illness. CBT has made him open … he has accepted it. It has helped him get better. He has learned so much CBT. He has almost become a psychiatrist … He recognizes his symptoms and he uses the right methods to deal with it from his tool box.*

> *I definitely think it's helpful, yes. I think it's very useful to challenge your ways of thinking, and not just for psychosis, but it's useful for a lot of different illnesses, yeah, to challenge your way of thinking and think a different way.*

> *Well, it opened me up to what was really going on and it made me understand what was happening. [New psychiatrist] gave me ways to cope and it's really helped my life a lot. I'm able to understand now that the problems are just fictional and that they'll just go away and that there's no sense getting all worked up about it. So, I'm really doing better now but not before; I didn't have those tools.*

This effectiveness relied upon two factors. First, patient and families insisted that CBT could only be effective in combination with medication. Neither treatment alone could be as effective as the two together. Second, due to the interpersonal nature of psychotherapy, patients reported feeling that its effectiveness often depended on the health care practitioner who was providing the therapy.

> *Without the help of this particular psychiatrist, without the methods of CBT… with just medication, he could not have done it. He could not have tremendous insight he currently has in his illness that he now has because of CBT.*

> *Cognitive behavioural therapy, I've been using it, I learned about it from my psychiatrist and I know a fair bit about it and I've been using it for the past eight years and it's amazing. I mean, the whole idea with CBT is to get cognitive restructuring, where you start to think in terms of, logically; you start to think logically and your anxiety and all that goes down. And CBT can be used with delusions because you can do thought records to challenge the delusions. It's really a wonderful thing. It is not a replacement for medicine, but once you have medicine, it can be used to foster rational thinking.*

Patients and families felt that effective psychotherapy, along with medication, could allow those living with psychosis and schizophrenia to return to being productive members of society. Families reported feeling that much of the burden and stress they had experienced could be lifted through this effective treatment. Several patients and family members also spoke of the improved quality of life in multiple areas, including work life, family life, and relationships with friends and family.

> *Providing this kind of help has allowed him to become a productive member of the society and will be making money and paying taxes. By paying for this service … government will actually save money in the long run.*

> *Real benefit of CBT starts with acceptance … he still has lots of anxiety. It will reduce in time and what is happening a life. He needs, stress levels need to be on an even keel … Every time he is able to deal with a particular challenge, … he feels empowered. All these things help him feel better about himself. Every little success is a huge thing.*

> *He has a part-time job now which I think is the best for him, because he's not working eight hours a day, seven days a week. So he has a chance to work and relax and see his children. So that's working very well for him.*

> *My parents were always supportive, they did more, I forgot to mention them actually, they did more than any parent, any child could ever ask for, my parents. They moved mountains to get me medical help. I mean, without my parents this recovery would not have been possible; it wouldn't have started it all.*

Discussion

We interviewed both patients and families concerning the challenges of living with schizophrenia and psychosis, its impact on their quality of life, and the perceived benefits of treatments such as cognitive behavioural therapy. By speaking with patients who had dealt with mental health challenges for years, along with parents of patients with schizophrenia and psychosis, we were able to hear a variety of perspectives on the challenges of this illness. Both groups reported consistently on the negative impact that schizophrenia and psychosis had on their quality of life for a number of years.

Additionally, several participants had lived in rural areas and were able to speak to the inequities in access to mental health services from these locations and the overall challenges in obtaining CBT for psychosis.

While the experiences with onset of schizophrenia were varied, patients and families reported similarly that denial of illness—the refusal to acknowledge a mental health condition—was a barrier to seeking treatment. Even after overcoming their denial, patients typically faced a long journey to obtain effective and sustainable treatment. The journey to treatment was accompanied by a sense of stigma and shame. Participants were consistent and clear in their perception that medication was necessary to allow those with schizophrenia to accept further treatment such as CBT for psychosis, and that CBT for psychosis would not be effective without medication as a co-treatment.

All patients and families interviewed were familiar with CBT for psychosis, and a majority had direct experience with it. All reported positive outcomes from this treatment, with increased quality of life and improvements in social and familial relationships. However, few commented on the nature of the health care practitioner who provided CBT for psychosis. Typically, this was a psychiatrist; participants were not able to comment on the effectiveness of CBT for psychosis from other types of health care practitioners. Commonly, access to this therpay was challenging, with long wait times and large costs associated with faster access; several patients and families reported moving to larger urban centres in the hope of reducing the wait for effective CBT for psychosis.

Conclusions

Patients with schizophrenia and their family members reported positive experiences with cognitive behavioural therapy, feeling that it provided effective tools to help manage this challenging mental health condition. Patients and families also felt that CBT for psychosis was only effective in conjunction with medication to help control psychotic episodes and other symptoms. They also reported that large barriers exist to accessing CBT for psychosis, including a patient's denial of illness, as well as geographic and financial barriers.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

Based on evidence of moderate to adequate quality as assessed by published systematic reviews, cognitive behavioural therapy (CBT) for psychosis in adults with schizophrenia significantly improved overall psychotic symptoms, positive symptoms, auditory hallucinations, delusions, and negative symptoms, when CBT for psychosis was compared with usual care or any control. Compared with other forms of psychotherapy, CBT for psychosis showed inconsistent results.

Less evidence was available on the best format or delivery model for this type of psychotherapy: Brief or low-intensity CBT for psychosis significantly improved overall psychotic symptoms and social function at follow-up, according to one systematic review of studies assessed as moderate or adequate quality. Group versus individual therapy did not significantly affect outcomes. We found no systematic reviews that compared physician and nonphysician service providers, providers by level of experience or training, or online and in-person delivery of CBT for psychosis.

Our economic modelling showed that adding CBT for psychosis in addition to usual care (including antipsychotic medication) probably represents good value for money in Ontario. It was cost-effective at various willingness-to-pay amounts when delivered by any type of certified, regulated health care provider, although physician therapists would be more costly than nonphysicians. In our model, the psychotherapy included treatment for first-episode psychosis plus a second course of CBT sessions for people experiencing relapse or treatment-resistant disease. We assumed that access to CBT for psychosis would increase gradually over a 5-year period until it was available to anyone newly diagnosed with schizophrenia—more than 8,000 adults each year.

Assuming CBT for psychosis is provided to 20% of eligible patients in the first year, with subsequent increases of 20% per year (to 100% in year 5), it would cost Ontario an additional $15.2 million over the next 5 years to publicly fund this therapy if it were provided by certified, regulated nonphysicians or about $35.4 million if provided by psychiatrists. Approximately 110 nonphysician therapists or 150 physicians trained in CBT for psychosis would be needed to provide full access to this therapy to about 12,000 adults with schizophrenia (including about 8,500 incident cases) over the next 5 years.

In interviews with us, patients and family members reported positive experiences with CBT for psychosis. They felt it provided effective tools to help manage schizophrenia but stressed it seemed effective only when used with antipsychotic medication. However, geographic and financial barriers have sometimes made this psychotherapy difficult or impossible to access.

ABBREVIATIONS

AMSTAR	Assessment of Multiple Systematic Reviews
BAVQ-R	Beliefs About Voices Questionnaire
BRPS	Brief Psychiatric Rating Scale
CADTH	Canadian Agency for Drugs and Technology in Health
CBT	Cognitive behavioural therapy
CI	Confidence interval
CPRS	Comprehensive Psychopathology Rating Scale
CrI	Credible interval
FTE	Full-time equivalent
GAF	Global Functioning Scale
GAS	Global Assessment Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
MMDAS	MacArthur-Maudsley Delusions Assessment Schedule
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PANSS	Positive and Negative Syndrome Scale
PDI	Peters Delusion Inventory
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSYRATS	Psychotic Symptom Rating Scales
QALY	Quality-adjusted life year
QLS	Quality of Life Scale
QSQ	Quality of Life Enjoyment and Satisfaction Questionnaire
RCT	Randomized controlled trial
ROBIS	Risk of Bias in Systematic Reviews
RR	Relative risk
SANS	Scale for Assessment of Negative Symptoms
SAPS	Schedule for the Assessment of Positive Symptoms
SD	Standard deviation
SFS	Social Functioning Scale
SGA	Second-generation antipsychotic (medication)
SMD	Standardized mean difference
SOFAS	Social and Occupational Functioning Assessment Scale
SPS	Social Provisions Scale
WHOQOL	World Health Organization Quality of Life scale

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: March 28, 2017
Databases searched: Ovid MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, and CINAHL

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 22, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 13>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>, PsycINFO <1967 to March Week 3 2017>
Search Strategy:
---
1 exp Schizophrenia/ (352458)
2 Schizotypal Personality Disorder/ (6417)
3 Schizoid Personality Disorder/ (3742)
4 (schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid).ti,ab,kf. (371065)
5 Psychotic Disorders/ (61707)
6 (psychos#s or psychotic).ti,ab,kf. (199491)
7 Delusions/ (20573)
8 delusion*.ti,ab,kf. (35366)
9 Hallucinations/ (26336)
10 hallucination*.ti,ab,kf. (39436)
11 or/1-10 (608668)
12 exp Cognitive Therapy/ (85259)
13 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).ti,ab,kf. (146754)
14 or/12-13 (180025)
15 11 and 14 (12989)
16 Meta Analysis.pt. (77683)
17 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (295178)
18 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (593427)
19 (meta analy* or metaanaly* or health technolog* assess*).mp. (408929)
20 or/16-19 (821924)
21 15 and 20 (1278)
22 21 use ppez,cctr,clhta,cleed (329)
23 15 use coch (19)
24 or/22-23 (348)
25 limit 24 to english language [Limit not valid in CDSR; records were retained] (310)

26 exp schizophrenia/ (352458)
27 schizotypal personality disorder/ (6417)
28 schizoidism/ (2656)
29 (schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid).tw,kw. (380395)
30 psychosis/ (149841)
31 (psychos#s or psychotic).tw,kw. (202839)
32 delusion/ (26974)
33 delusion*.tw,kw. (36490)
34 hallucination/ (37075)
35 hallucination*.tw,kw. (40647)
36 or/26-35 (632343)
37 exp cognitive therapy/ (85259)
38 exp cognitive behavioral therapy/ (31000)
39 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).tw,kw,dv. (156133)
40 or/37-39 (188277)
41 36 and 40 (14503)
42 Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (287381)
43 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (593427)
44 (meta analy* or metaanaly* or health technolog* assess*).mp. (408929)
45 or/42-44 (820645)
46 41 and 45 (1627)
47 limit 46 to english language [Limit not valid in CDSR; records were retained] (1498)
48 47 use emez (709)
49 exp schizophrenia/ (352458)
50 schizoaffective disorder/ (54791)
51 schizoid personality disorder/ (3742)
52 schizotypal personality disorder/ (6417)
53 schizotypy/ (758)
54 (schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid).ti,ab,id. (370380)
55 psychosis/ (149841)
56 (psychos#s or psychotic).ti,ab,id. (196157)
57 delusions/ (20573)
58 delusion*.ti,ab,id. (35324)
59 hallucinations/ (26336)
60 hallucination*.ti,ab,id. (39152)
61 or/49-60 (623560)
62 exp cognitive behavior therapy/ (47738)
63 cognitive therapy/ (83094)
64 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).ti,ab,id. (149755)
65 or/62-64 (183863)
66 61 and 65 (13584)
67 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed

or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (593427)
68 (meta analy* or metaanaly* or health technolog* assess*).mp. (408929)
69 (systematic review or meta analysis).md. (30043)
70 or/67-69 (806815)
71 66 and 70 (1327)
72 limit 71 to english language [Limit not valid in CDSR; records were retained] (1200)
73 72 use psyb (226)
74 25 or 48 or 73 (1245)
75 74 use ppez (260)
76 74 use emez (709)
77 74 use psyb (226)
78 74 use coch (19)
79 74 use cctr (27)
80 74 use clhta (4)
81 74 use cleed (0)
82 remove duplicates from 74 (855)

CINAHL

#	Query	Results
S1	(MH "Schizophrenia+")	18,326
S2	(MH "Schizotypal Personality Disorder")	210
S3	(MH "Schizoaffective Disorder")	143
S4	(schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid)	23,095
S5	(MH "Psychotic Disorders")	7,913
S6	(psychos?s or psychotic)	14,505
S7	(MH "Delusions")	1,260
S8	delusion*	2,334
S9	(MH "Hallucinations+")	2,027
S10	hallucination*	3,122
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	35,501
S12	(MH "Cognitive Therapy+")	15,073
S13	(((cognitive or behavio*) N2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp)	35,232
S14	S12 OR S13	36,503
S15	S11 AND S14	1,896
S16	(MH "Meta Analysis")	26,766
S17	(PT "Meta Analysis") or (PT "Systematic Review")	57,193
S18	((systematic* or methodologic*) N3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* N1 (assessment* or overview* or appraisal*))	121,165
S19	S16 OR S17 OR S18	131,161
S20	S15 AND S19	176
S21	S15 AN S19 Limiters - English Language	175

Economic Evidence Search

Economic Evaluation and Cost-Effectiveness Search
Search date: April 5, 2017
Databases searched: Ovid MEDLINE, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 4, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 14>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>, PsycINFO <1967 to March Week 4 2017>
Search Strategy:
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1 exp Schizophrenia/ (352912)
2 Schizotypal Personality Disorder/ (6433)
3 Schizoid Personality Disorder/ (3748)
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5 Psychotic Disorders/ (61726)
6 (psychos#s or psychotic).ti,ab,kf. (199798)
7 Delusions/ (20577)
8 delusion*.ti,ab,kf. (35405)
9 Hallucinations/ (26345)
10 hallucination*.ti,ab,kf. (39499)
11 or/1-10 (609535)
12 exp Cognitive Therapy/ (85525)
13 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).ti,ab,kf. (147174)
14 or/12-13 (180528)
15 11 and 14 (13016)
16 economics/ (272895)
17 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (793424)
18 economics.fs. (396321)
19 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (878172)
20 exp "costs and cost analysis"/ (565944)
21 (cost or costs or costing or costly).ti. (242220)
22 cost effective*.ti,ab,kf. (277014)
23 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (185518)
24 models, economic/ (173356)
25 markov chains/ or monte carlo method/ (71451)
26 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (37413)
27 (markov or markow or monte carlo).ti,ab,kf. (114649)
28 quality-adjusted life years/ (33586)

29 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (59005)
30 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (93277)
31 or/16-30 (2573844)
32 15 and 31 (829)
33 32 use ppez,coch,cctr,clhta (246)
34 15 use cleed (10)
35 or/33-34 (256)
36 limit 35 to english language [Limit not valid in CDSR; records were retained] (227)
37 exp schizophrenia/ (352912)
38 schizotypal personality disorder/ (6433)
39 schizoidism/ (2662)
40 (schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid).tw,kw. (380997)
41 psychosis/ (150081)
42 (psychos#s or psychotic).tw,kw. (203166)
43 delusion/ (27007)
44 delusion*.tw,kw. (36532)
45 hallucination/ (37135)
46 hallucination*.tw,kw. (40714)
47 or/37-46 (633274)
48 exp cognitive therapy/ (85525)
49 exp cognitive behavioral therapy/ (31088)
50 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).tw,kw,dv. (156576)
51 or/48-50 (188808)
52 47 and 51 (14535)
53 Economics/ (272895)
54 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (131237)
55 Economic Aspect/ or exp Economic Evaluation/ (434343)
56 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (906383)
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61 Monte Carlo Method/ (57587)
62 (decision adj1 (tree* or analy* or model*)).tw,kw. (41383)
63 (markov or markow or monte carlo).tw,kw. (119897)
64 Quality-Adjusted Life Years/ (33586)
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67 or/53-66 (2082676)
68 52 and 67 (1148)
69 limit 68 to english language [Limit not valid in CDSR; records were retained] (1074)
70 69 use emez (423)
71 exp schizophrenia/ (352912)
72 schizoaffective disorder/ (54831)
73 schizoid personality disorder/ (3748)

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78 (psychos#s or psychotic).ti,ab,id. (196468)
79 delusions/ (20577)
80 delusion*.ti,ab,id. (35366)
81 hallucinations/ (26345)
82 hallucination*.ti,ab,id. (39216)
83 or/71-82 (624460)
84 exp cognitive behavior therapy/ (47884)
85 cognitive therapy/ (83344)
86 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).ti,ab,id. (150171)
87 or/84-86 (184395)
88 83 and 87 (13612)
89 economics/ or economy/ (380112)
90 pharmacoeconomics/ or health care economics/ (175762)
91 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (882776)
92 exp "costs and cost analysis"/ (565944)
93 cost*.ti. (262355)
94 cost effective*.tw. (284572)
95 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (185518)
96 markov chains/ (16447)
97 (decision adj1 (tree* or analy* or model*)).tw. (40558)
98 (markov or markow or monte carlo).tw. (117582)
99 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (62222)
100 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (111106)
101 or/89-100 (1999003)
102 88 and 101 (746)
103 limit 102 to english language [Limit not valid in CDSR; records were retained] (674)
104 103 use psyb (103)
105 36 or 70 or 104 (753)
106 105 use ppez (153)
107 105 use emez (423)
108 105 use psyb (103)
109 105 use coch (4)
110 105 use cctr (59)
111 105 use cleed (10)
112 105 use clhta (1)
113 remove duplicates from 105 (547)

CINAHL

#	Query	Results
S1	(MH "Schizophrenia+")	18,343
S2	(MH "Schizotypal Personality Disorder")	210
S3	(MH "Schizoaffective Disorder")	143
S4	(schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid)	23,123
S5	(MH "Psychotic Disorders")	7,922
S6	(psychos?s or psychotic)	14,525
S7	(MH "Delusions")	1,259
S8	delusion*	2,333
S9	(MH "Hallucinations+")	2,029
S10	hallucination*	3,125
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	35,547
S12	(MH "Cognitive Therapy+")	15,103
S13	(((cognitive or behavio*) N2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp)	35,278
S14	S12 OR S13	36,561
S15	S11 AND S14	1,897
S16	(MH "Economics")	11,114
S17	(MH "Economic Aspects of Illness")	6,670
S18	(MH "Economic Value of Life")	519
S19	MH "Economics, Dental"	104
S20	MH "Economics, Pharmaceutical"	1,777
S21	MW "ec"	141,598
S22	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	212,244
S23	(MH "Costs and Cost Analysis+")	84,829
S24	TI cost*	39,961
S25	(cost effective*)	27,211

S26	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	18,024
S27	(decision N1 (tree* or analy* or model*))	4,968
S28	(markov or markow or monte carlo)	3,096
S29	(MH "Quality-Adjusted Life Years")	2,635
S30	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	5,803
S31	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analys?s)	11,151
S32	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	282,946
S33	S15 AND S32	82
S34	S15 AND S32 Limiters - English Language	82

Health State Utility Value Search
Search date: April 6, 2017

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 exp Schizophrenia/ (96648)
2 Schizotypal Personality Disorder/ (2440)
3 Schizoid Personality Disorder/ (596)
4 (schizophreni* or schizotyp* or schizoaffective or schizo-affective or schizoid).ti,ab,kf. (114568)
5 Psychotic Disorders/ (41700)
6 (psychos#s or psychotic).ti,ab,kf. (61736)
7 Delusions/ (7379)
8 delusion*.ti,ab,kf. (9936)
9 Hallucinations/ (10092)
10 hallucination*.ti,ab,kf. (11785)
11 or/1-10 (194499)
12 exp Cognitive Therapy/ (22390)
13 (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT or CBTp).ti,ab,kf. (34650)
14 or/12-13 (43663)
15 11 and 14 (3013)
16 Quality-Adjusted Life Years/ (9417)
17 (quality adjusted or adjusted life year*).tw. (12117)
18 (qaly* or qald* or qale* or qtime*).tw. (7833)
19 (illness state$1 or health state$1).tw. (5239)
20 (hui or hui1 or hui2 or hui3).tw. (1199)
21 (multiattribute* or multi attribute*).tw. (709)
22 (utility adj3 (score$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).tw. (11099)
23 utilities.tw. (5638)
24 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).tw. (7559)
25 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw. (2560)
26 (sf36* or sf 36* or sf thirtysix or sf thirty six).tw. (18545)
27 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw. (1603)
28 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change$1 or impact$1 or impacted or deteriorate$)).ab. (23961)
29 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).tw. (2536)
30 *quality of life/ and (quality of life or qol).ti. (43728)
31 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).tw. (19006)
32 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).tw. (9446)
33 quality of life/ and health-related quality of life.tw. (23828)
34 quality of life/ and ec.fs. (8618)

35 quality of life/ and (health adj3 status).tw. (7323)
36 (quality of life or qol).tw. and cost-benefit analysis/ (9629)
37 models, economic/ (8239)
38 or/16-37 (126187)
39 15 and 38 (55)
40 limit 39 to english language (52)

Grey Literature
Performed on:
March 30–April 4, 2017
Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Prospero, Tufts Cost Effectiveness Analysis Registry

Keywords used:
Cognitive, CBT, behavior, behaviour, behavioral, behavioural, counseling, psychosis, schizophrenia, thérapie cognitivo-comportementale, psychose, schizophrénie

Results: 4

Appendix 2: Clinical Evidence Quality Assessment

Table A1: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Alvarez-Jimenez et al, 2011[46]	8	✗	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗
Baandrup et al, 2016[47]	7	✗	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗
Hazell et al, 2016[48]	7	✗	✗	✓	✓	✗	✓	✓	✓	✓	✓	✗
Jauhar et al, 2014[58]	9	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Jones et al, 2012[49]	10	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Kennedy and Xyrichis, 2017[50]	7	✗	✗	✓	✓	✗	✓	✓	✓	✓	✗	✓
Lutgens et al, 2017[51]	9	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗
Marshall and Rathbone, 2011[52]	10	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Naeem et al, 2015[53]	6	✗	✓	✓	✓	✗	✓	✗	✗	✓	✓	✗
Turner et al, 2014[54]	6	✗	✓	✗	✗	✗	✓	✓	✓	✓	✓	✗
van der Gaag et al, 2014[55]	6	✗	✗	✓	✗	✗	✓	✓	✓	✓	✓	✗
Velthorst et al, 2015[56]	7	✗	✗	✓	✓	✗	✓	✓	✓	✓	✓	✗
Wykes et al, 2008[57]	7	✗	✓	✓	✗	✗	✓	✓	✓	✓	✓	✗

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews.

[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al.[43]

Note: ✓ means the systematic review addressed this item. ✗ means the systematic review did not address this item.

Table A2: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

Author, Year	Phase 2				Phase 3
	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Alvarez-Jimenez et al, 2011[46]	Low	Low	Low	Low	Low
Baandrup et al, 2016[47]	Low	High[b]	Low	Low	Low
Hazell et al, 2016[48]	Low	High[c]	High[d]	Low	High
Jauhar et al, 2014[58]	Low	Low	Low	Low	Low
Jones et al, 2012[49]	Low	Low	Low	Low	Low
Kennedy and Xyrichis, 2017[50]	Low	High[c]	Low	Low	Low
Lutgens et al, 2017[51]	Low	High[b]	Low	Low	Low
Marshall and Rathbone, 2011[52]	Low	Low	Low	Low	Low
Naeem et al, 2015[53]	Low	Low	Low	Low	Low
Turner et al, 2014[54]	Low	High[b]	Low	Low	Low
van der Gaag et al, 2014[55]	Low	High[c]	Low	Low	Low
Velthorst et al, 2015[56]	Low	High[b]	Low	Low	Low
Wykes et al, 2008[57]	Low	Low	High[e]	Low	Low

Abbreviation: ROBIS, Risk of Bias in Systematic Reviews.
[a]Possible risk of bias levels: low, high, unclear.
[b]Potential bias due to language restrictions.
[c]Potential bias due to single reviewer for study selection.
[d]Potential bias due to single reviewer for data extraction.
[e]Limited study characteristics provided to allow interpretation of results.

Appendix 3: Excluded Studies

For transparency, we provide this list of related studies that readers might expect to see but that did not meet the inclusion criteria of our clinical evidence review, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Alvarez-Jimenez M, Alcazar-Corcoles MA, Gonzalez-Blanch C, Bendall S, McGorry PD, Gleeson JF. Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. Schizophr Res. 2014;156(1):96-106.	No comparator group
Armando M, Pontillo M, Vicari S. Psychosocial interventions for very early and earlyonset schizophrenia: a review of treatment efficacy. Curr Opin Psychiatry. 2015;28(4):312-23.	Not population of interest
Armijo J, Mendez E, Morales R, Schilling S, Castro A, Alvarado R, et al. Efficacy of community treatments for schizophrenia and other psychotic disorders: a literature review. Front Psychiatry. 2013;4:116.	Did not meet definition of systematic review (narrative review)
Bird V, Premkumar P, Kendall T, Whittington C, Mitchell J, Kuipers E. Early intervention services, cognitive-behavioural therapy and family intervention in early psychosis: systematic review. Br J Psychiatry. 2010;197(5):350-6.	Did not meet definition of systematic review (no quality assessment)
Burns AMN, Erickson DH, Brenner CA. Cognitive-behavioral therapy for medication-resistant psychosis: a meta-analytic review. Psychiatr Serv. 2014;65(7):874-80.	Did not meet definition of systematic review (no quality assessment)
Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev. 2006;26(1):17-31.	Overview of reviews
Canadian Agency for Drugs and Technologies in Health. Group therapy in the treatment of schizophrenia: a review of the clinical effectiveness [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.	Did not meet definition of systematic review (narrative review)
Castelein S, Knegtering H. Treatment of negative symptoms: which psychosocial interventions are effective? Schizophr Bull. 2011;37:261.	Conference abstract
Chien WT, Leung SF, Yeung FKK, Wong WK. Current approaches to treatments for schizophrenia spectrum disorders, part II: psychosocial interventions and patient-focused perspectives in psychiatric care. Neuropsychiatr Dis Treat. 2013;9:1463-81.	Did not meet definition of systematic review (narrative review)
Cooke C, Heatley R, Galani Berardo C, Johnson KI, Kasper S. Clinical outcomes assessments in schizophrenia: a systematic literature review. Value Health. 2013;16 (7):A575.	Conference abstract
Cormac I, Jones C, Campbell C. Cognitive behaviour therapy for schizophrenia. Cochrane Database Syst Rev. 2002(1):CD000524.	Superseded review
Draper ML, Velligan DI, Tai S. Cognitive behavioral therapy for schizophrenia: a review of recent literature and meta-analyses. Minerva Psichiatr. 2010;51(2):85-94.	Did not meet definition of systematic review (narrative review)
Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry. 2015;50(5):410-72.	Did not meet definition of systematic review (narrative review)
Gaudiano BA. Is symptomatic improvement in clinical trials of cognitive-behavioral therapy for psychosis clinically significant? J Psychiatr Pract. 2006;12(1):11-23.	Did not meet definition of systematic review (narrative review)
Gould RA, Mueser KT, Bolton E, Mays V, Goff D. Cognitive therapy for psychosis in schizophrenia: an effect size analysis. Schizophr Res. 2001;48(2-3):335-42.	Not clear if CBT for psychosis
Guaiana G, Morelli CA, Chiodo D. Cognitive behaviour therapy (group) for schizophrenia. Cochrane Database Syst Rev. 2012(2).	Protocol only
Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cognit Ther Res. 2012;36(5):427-40.	Overview of reviews
Hunter ECM, Johns LC, Onwumere J, Peters E. Cognitive behavioural therapy for psychosis. Treatment-refractory schizophrenia: a clinical conundrum. New York, NY: Springer-Verlag Publishing; US; 2014. p. 139-64.	Did not meet definition of systematic review (narrative review)
Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychol Med. 2014;44(3):449-68.	Not population of interest

Citation	Primary Reason for Exclusion
Hutton P, Wood L, Taylor PJ, Irving K, Morrison AP. Cognitive behavioural therapy for psychosis: rationale and protocol for a systematic review and meta-analysis. Psychosis. 2014;6(3):220-30.	Protocol only
Ince P, Haddock G, Tai S. A systematic review of the implementation of recommended psychological interventions for schizophrenia: rates, barriers, and improvement strategies. Psychol Psychother. 2016;89(3):324-50.	Not outcomes of interest
Jones C, Campbell C, Cormac I, Hacker D, Meaden A. Cognitive behaviour therapy versus standard care for schizophrenia. Cochrane Database Syst Rev. 2009(3):CD007964.	Protocol only
Jones C, Cormac I, Campbell C, Meaden A, Hacker D. Cognitive behaviour therapy versus specific pharmacological treatments for schizophrenia. Cochrane Database Syst Rev. 2009(3):CD007965.	Protocol only
Jones C, Cormac I, Silveira da Mota Neto JI, Campbell C. Cognitive behaviour therapy for schizophrenia. Cochrane Database Syst Rev. 2004(4):CD000524.	Superseded review
Jones C, Hacker D, Cormac I, Meaden A, Irving CB. Cognitive behavior therapy versus other psychosocial treatments for schizophrenia. Schizophr Bull. 2012;38(5):908-10.	Duplicate publication
Jones C, Hacker D, Meaden A, Cormac I, Irving CB. Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. Cochrane Database Syst Rev. 2011(4):CD000524.	Superseded review
Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. Contemp Clin Trials. 2014;38(1):1-8.	Data on CBTp not presented / could not be extracted
Junghan UM, Pfammatter M. What are the therapeutic ingredients of cognitive behavior therapy for psychosis? A systematic review. Eur Arch Psychiatry Clin Neurosci. 2011;261:S36.	Conference abstract
Lawrence R, Bradshaw T, Mairs H. Group cognitive behavioural therapy for schizophrenia: a systematic review of the literature. J Psychiatr Ment Health Nurs. 2006;13(6):673-81.	Did not meet definition of systematic review (no quality assessment)
Lim C, Sim K, Renjan V, Sam HF, Quah SL. Adapted cognitive-behavioral therapy for religious individuals with mental disorder: a systematic review. Asian J Psychiatr. 2014;9:3-12.	No data on outcomes of interest presented
Liu P, Parker AG, Hetrick SE, Callahan P, de Silva S, Purcell R. An evidence map of interventions across premorbid, ultra-high risk and first episode phases of psychosis. Schizophr Res. 2010;123(1):37-44.	Did not meet definition of systematic review (narrative review)
Lockwood C, Page T, Conroy-Hiller T. Systematic review: effectiveness of individual therapy and group therapy in the treatment of schizophrenia. JBI Reports. 2004;2(4):309-38.	Not entirely CBT for psychosis as intervention
Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychol Med. 2010;40(1):9-24.	Did not meet definition of systematic review (no reproducible search strategy)
Mehl S, Werner D, Lincoln TM. Does cognitive behavior therapy for psychosis (CBTp) show a sustainable effect on delusions? A meta-analysis. Front Psychol. 2015;6:1450.	Did not meet definition of systematic review (no quality assessment)
Morrison AP. Cognitive behaviour therapy for first episode psychosis: good for nothing or fit for purpose? Psychosis. 2009;1(2):103-12.	No data on outcomes of interest presented
Naeem F, Farooq S, Kingdon D. Cognitive behavioral therapy (brief vs standard duration) for schizophrenia. Schizophr Bull. 2014;40(5):958-9.	Duplicate publication
Naeem F, Farooq S, Kingdon D. Cognitive behavioural therapy (brief versus standard duration) for schizophrenia. Cochrane Database Syst Rev. 2014(4):CD010646.	Superseded review
National Collaborating Centre for Mental Health. Psychosis and schizophrenia in adults: treatment and management. National clinical guideline number 178 [Internet]. London (UK): National Institute for Health and Care Excellence; 2014.	Did not meet definition of systematic review (no quality assessment)
Newton-Howes G, Wood R. Cognitive behavioural therapy and the psychopathology of schizophrenia: systematic review and meta-analysis. Psychology and psychotherapy. 2013;86(2):127-38.	Did not meet definition of systematic review (no quality assessment)
Niemeyer H, Musch J, Pietrowsky R. Publication bias in meta-analyses of the efficacy of psychotherapeutic interventions for schizophrenia. Schizophr Res. 2012;138(2-3):103-12.	Not outcomes of interest
Nowak I, Sabariego C, Switaj P, Anczewska M. Disability and recovery in schizophrenia: a systematic review of cognitive behavioral therapy interventions. BMC Psychiatry. 2016;16:228.	Not outcomes of interest

Citation	Primary Reason for Exclusion
O'Keeffe J, Conway R, McGuire B. A systematic review examining factors predicting favourable outcome in cognitive behavioural interventions for psychosis. Schizophr Res. 2016;23:23.	Not outcomes of interest
Orfanos S, Banks C, Priebe S. Are group psychotherapeutic treatments effective for patients with schizophrenia? A systematic review and meta-analysis. Psychother Psychosom. 2015;84(4):241-9.	Data on CBTp not presented / could not be extracted
Perez PV, De Azua SR, Martinez M, Ron S, Oliveros RG, Asua J, et al. Psychological treatment in the first psychotic episode. Eur Neuropsychopharmacol. 2009;19:S483-S4.	Conference abstract
Pfammatter M. The empirical status of CBT for psychosis: controlled efficacy, indication and therapeutic factors. A systematic review of metaanalytic findings. European Psychiatry Conference: 19th European Congress of Psychiatry, EPA. 2011;26(no pagination).	Conference abstract
Pfammatter M, Junghan UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. Schizophr Bull. 2006;32 Suppl 1:S64-80.	Overview of reviews
Pilling S, Bebbington P, Kuipers E, Garety P, Geddes J, Orbach G, et al. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. Psychol Med. 2002;32(5):763-82.	Did not meet definition of systematic review (no quality assessment or reproducible search strategy)
Pitkanen A, Puolakka K. Effectiveness of psychological and psychosocial interventions on quality of life of patients with schizophrenia and related disorders: a systematic review protocol. JBI Database of Systematic Reviews and Implementation Reports. 2013;11(6):157-68.	Protocol only
Pontillo M, De Crescenzo F, Vicari S, Pucciarini ML, Averna R, Santonastaso O, et al. Cognitive behavioural therapy for auditory hallucinations in schizophrenia: a review. World J Psychiatry. 2016;6(3):372-80.	Did not meet definition of systematic review (narrative review)
Rathod S, Kingdon D, Weiden P, Turkington D. Cognitive-behavioral therapy for medication-resistant schizophrenia: a review. J Psychiatr Pract. 2008;14(1):22-33.	Did not meet definition of systematic review (narrative review)
Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust N Z J Psychiatry. 2005;39(1-2):1-30.	Superseded review
Sarin F, Wallin L. Cognitive model and cognitive behavior therapy for schizophrenia: an overview. Nord J Psychiatry. 2014;68(3):145-53.	Did not meet definition of systematic review (only one database searched)
Sarin F, Wallin L, Widerlov B. Cognitive behavior therapy for schizophrenia: a meta-analytical review of randomized controlled trials. Nord J Psychiatry. 2011;65(3):162-74.	Did not meet definition of systematic review (quality assessment not presented by study)
Segredou I, Xenitidis K, Panagiotopoulou M, Bochtsou V, Antoniadou O, Livaditis M. Group psychosocial interventions for adults with schizophrenia and bipolar illness: the evidence base in the light of publications between 1986 and 2006. Int J Soc Psychiatry. 2012;58(3):229-38.	No data on outcomes of interest presented
Seppala A, Miettunen J, Hirvonen N, Isohanni M, Moilanen J, Koponen H, et al. What do we know about treatment-resistant schizophrenia? A systematic review. Eur Psychiatry. 2016;33:S586.	Conference abstract
Sinclair D, Adams CE. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. BMC Psychiatry. 2014;14:253.	Did not meet definition of systematic review (narrative review)
Sivec HJ, Montesano VL. Cognitive behavioral therapy for psychosis in clinical practice. Psychotherapy. 2012;49(2):258-70.	Did not meet definition of systematic review (narrative review)
Smith TE, Weston CA, Lieberman JA. Schizophrenia (maintenance treatment). Clin Evid. 2009;16:16.	Did not meet definition of systematic review (no reproducible search strategy)
Stafford MR, Mayo-Wilson E, Loucas CE, James A, Hollis C, Birchwood M, et al. Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: a systematic review and meta-analysis. PLoS ONE [Electronic Resource]. 2015;10(2):e0117166.	Not population of interest

Citation	Primary Reason for Exclusion
Steel C, Stahl D, Tarrier N, Wykes T. How effective is CBTp and does this depend on your therapist? Schizophr Res. 2010;117 (2-3):159.	Conference abstract
Tsapakis EM, Dimopoulou T, Tarazi FI. Clinical management of negative symptoms of schizophrenia: an update. Pharmacol Ther. 2015;153:135-47.	Did not meet definition of systematic review (narrative review)
Tundo A, Necci R. Cognitive-behavioural therapy for obsessive-compulsive disorder co-occurring with psychosis: systematic review of evidence. World J Psychiatry. 2016;6(4):449-55.	Not CBT for psychosis
Van Der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. Schizophr Res. 2013;149(1-3):56-62.	Not population of interest
Wood L, Burke E, Morrison A. Individual cognitive behavioural therapy for psychosis (CBTp): a systematic review of qualitative literature. Behav Cogn Psychother. 2015;43(3):285-97.	Not outcomes of interest
Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. Schizophr Res. 2005;77(1):1-9.	Did not meet definition of systematic review (no quality assessment)

Appendix 4: Characteristics of Included Systematic Reviews

Table A3: Characteristics of Included Systematic Reviews

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
Alvarez-Jimenez et al, 2011[46]	To undertake a systematic review and meta-analysis of all relevant RCTs of pharmacological and nonpharmacological interventions to prevent relapse in patients with first-episode psychosis	To December 2008 • Cochrane Central Register of Controlled Trials • MEDLINE & MEDLINE Unindexed • Embase • PsycINFO • UMI Proquest Digital Dissertations • Information Science Citation Index Expanded • Information Social Sciences Citation Index • Information Arts and Humanities Citation Index • Conference abstracts from ISI Science and Technology proceedings and ISI Information Social Science and Humanities proceedings • Hand-searching reference lists of retrieved trials, previous reviews, and abstracts from meetings • Trialists and other experts were contacted for unpublished studies	RCTs	At least 75% of participants experiencing their first episode of psychosis diagnosed using either Diagnostic and Statistical Manual of Mental Disorders or International Classification of Drugs criteria	Nonpharmacological intervention (of which CBT for psychosis was one intervention)	Comparison interventions could include standard care, placebo, or an active comparator intervention	Primary: • Number of relapses Secondary: • Mean hospital days • Time to relapse • Duration of second episode Discontinuation of treatment due to adverse events	Cochrane Risk of Bias Tool
Baandrup et al, 2016[47]	What is the effect of cognitive behavioural therapy in patients with schizophrenia and functional impairment?	To December 2014 • Guidelines International Network • NICE • National Guideline Clearinghouse • Scottish Intercollegiate Guidelines Network • HTA database • SBU (Sweden)	RCTs	Adult patients with schizophrenia or other disorder in the schizophrenia disorder (ICD-10: F2) and inadequate response to antipsychotic treatment at the relevant dosage and duration	CBT of minimum 4-month duration; minimum of 10 sessions planned; therapists have formal education	Usual care (i.e., continued antipsychotic treatment without the addition of CBT)	At end of intervention: • Psychotic symptoms (20–25% reduction) • Negative symptoms (20–25% reduction) • Social function • Distress	GRADE

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
		• Socialstyrelsen (Sweden) • Helsedirektoratet (Norway) • Kunnskapssenteret (Norway) • MEDLINE • Embase • PsycINFO CINAHL					• Quality of life • Days in hospital At longest follow-up (minimum 4–6 months): • Psychotic symptoms • Negative symptoms	
Hazell et al, 2016[48]	To evaluate the effectiveness of low-intensity CBTp (i.e., CBTp delivered in fewer than the NICE-recommended 16 face-to-face therapy sessions)	To 10 December 2015 • PsycINFO • Web of Knowledge • Scopus • Screening of studies included in 2 major meta-analyses of CBTp Clinical Trials and ISRCTN research registries	Controlled trials	Participants with a psychotic disorder, as defined by NICE guidelines (2014), according to either DSM (American Psychiatric Association, 2013) or ICD (WHO, 1992) criteria Exclusion: when substance misuse was the primary mental health disorder	Low-intensity CBTp (defined as CBTp interventions designed with fewer than 16 sessions of face-to-face contact time) Exclusion: when CBTp was integrated with another psychological intervention, as it would not be possible to attribute outcomes to CBTp alone	Any	At least one quantitative measure of: • Psychosis • Depression • Anxiety Functioning	Downs and Black's Quality Index
Jauhar et al, 2014[58]	To examine the effectiveness of CBT for schizophrenic symptoms that includes an examination of potential sources of bias	March 2013 • MEDLINE (1993 to Week 3, March 2013), PsycINFO (1993 until Week 4, March 2013) • Embase (1993 until Week 4, March 2013) • Cochrane Central Register of Controlled Trials (1993 until end of March 2013) Hand-searching of meta-analyses and review articles	RCTs	Patients with a diagnosis of schizophrenia, schizoaffective or non-affective functional psychosis, either made clinically or according to diagnostic criteria	CBT (both individual and group) directed at least one class of schizophrenic symptoms CBT that incorporated additional elements of therapy such as MI, family engagement, behaviour therapy and social skills training were included	Any parallel control group (i.e., waitlist, usual care, or an intervention designed to control for the non-effects of psychotherapy)	Schizophrenia symptoms: • Overall symptoms • Positive symptoms • Negative symptoms	Examined three sources of bias: • Randomization • Masking • Incompleteness of outcome data

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
Jones et al, 2012[49]	To assess the effectiveness of adjunct CBT for people with schizophrenia compared with other adjunct psychosocial interventions	March 2010 • Cochrane Schizophrenia Group's Register (based on regular searches of BIOSIS Inside, CENTRAL, CINAHL, Embase, MEDLINE, and PsycINFO, hand-searching of relevant journals and conference proceedings, and searches of several key grey literature sources)	RCTs	People with a current diagnosis of schizophrenia, diagnosed by any criteria, irrespective of gender or race (more than 50% of the participants had a diagnosis of schizophrenia)	"Well-defined" CBT, defined as a discrete psychological intervention, which is in addition to, and separate from, other therapeutic interventions (for example, behavioural family therapy) and recipients establish links between their symptoms, thoughts and beliefs, and consequent distress or problem behaviour and the re-evaluation of their perceptions, beliefs or reasoning relating to the target symptoms	Other psychosocial interventions provided in addition to usual care or standard care	Primary • Death • Mental State Secondary • Mental state • Adverse effects • Engagement with services • Global state • Quality of life • Satisfaction with treatment • Economic	GRADE

Kennedy and Xyrichis, 2016[50]	To examine the evidence for the superiority of CBT compared to non-specialized therapy in alleviating auditory hallucinations in community patients with schizophrenia	To April 2015
		• Embase (1980 to Week 17, 2015)
		• MEDLINE (1946 to April Week 3, 2015)
		• PsycINFO (1806 to April Week 3, 2015)
		• Cochrane Library of Systematic Reviews (scoping search)
		• Reference lists of relevant articles
		• Further electronic searches:
		  ○ Web of Science
		  ○ EU Clinical Trials Register
		  ○ ClinicalTrials.gov
		  ○ International Clinical Trials Registry Platform
			RCTs	Adults with schizophrenia or schizoaffective disorder residing in the community with no ongoing medication or symptomatic concerns;
				Recruited participants must have had a recent history or an on-going presence of auditory hallucinations and being treated with antipsychotic medication
					Recognizable CBT techniques used for auditory hallucinations	Non-specialized therapy focused on supportive interactions and social integration	Auditory hallucinations	GRADE

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
Lutgens et al, 2017[51]	To conduct a meta-analytic and systematic review of the literature on the effectiveness of non-biological treatments for negative symptoms in psychotic disorders	To 19 October 2015 • MEDLINE via PubMed • Embase • Web of Science • PsycINFO • Cochrane Library • Hand-searches of bibliography from primary studies, review articles and key journals, as well as through contacts with experts in the field	RCTs	Majority sample with a diagnosis of a schizophrenia spectrum or other non-organic psychotic disorder	CBT	Usual care or other active psychological interventions	Negative symptoms	Critical appraisal checklist
Marshall and Rathbone, 2011[52]	To determine the effects of early detection and treatment of people in their first episode of psychosis, in terms of clinical and social outcomes, prevention of relapse, process variables and costs, and reduction in duration of untreated psychosis	To March 2009 • The Cochrane Schizophrenia Group's Register • CINAHL • The Cochrane Controlled Trials Register • Embase • MEDLINE • PyscINFO	RCTs	People who were in their first episode of psychosis or were in the process of recovering from their first episode; Where studies included both first and second episode participants, trial were excluded if > 10% of participants included in the study had experienced a second episode	CBT	Standard care or care from a specialized team	Primary • Relapse Secondary • Overall functioning • Hospital readmission • Duration of hospital stay • Loss to follow-up • Satisfaction with treatment (participant/carer) • Remaining in contact with services • General symptoms • Specific symptoms • Positive symptoms • Negative symptoms • Mood: depression • General behaviour • Specific behaviours • Social functioning • Employment status • Adverse events • Death (suicide and non-suicide)	Cochrane Risk of Bias Tool

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
Naeem et al, 2015[53]	To compare the effects of brief CBT for people with schizophrenia against standard CBT for schizophrenia.	To August 2013 • Cochrane Schizophrenia Group's Registry of Trials • Inspected the references of all identified studies for further relevant studies	RCTs	Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis	Brief CBT (defined as 6 to 10 sessions in less than 4 months and using a manual)	Standard CBT (defined as 12 to 20 sessions over 4 to 6 months)	Primary • Global state • Leaving the study early • Mental state • Service use • Quality of life Secondary • Death • General functioning • Satisfaction with treatment • Adverse effects • Economic costs	GRADE
Turner et al, 2014[54]	To provide further insight into the relative efficacy of psychological interventions for psychosis	May 2013 • PubMed • Embase • PsycINFO • Cochrane Central Register of Controlled Trials • Reference lists of published meta-analyses were also examined	RCTs	Primarily participants with diagnoses of psychotic disorders Trials that included patients with mood disorders with psychotic features were included only when such patients were in a minority within the sample	Active psychological interventions • Befriending • CBT • Cognitive remediation • Psychoeducation • Social skills training Supportive counselling	Active psychological interventions • Befriending • CBT • Cognitive remediation • Psychoeducation • Social skills training Supportive counselling	All symptoms Positive symptoms Negative symptoms	A modified Cochrane Risk of Bias Tool
van der Gaag et al, 2014[55]	To evaluate the end-of-treatment effects of individually tailored case-formulation cognitive behavioural therapy on delusions and auditory hallucinations using symptom-specific outcome measures	1987 to July 2013 • MEDLINE (1996 to July 2013) • Embase (1996 to July 2013) • PsycINFO (1987 to July 2013) • Also examined published reviews and meta-analyses	RCTs	Patients diagnosed with a psychotic disorder, with at least 75% schizophrenia patients	Formulation-based CBT for psychosis* **The criteria used to define individually tailored case-formulation CBT were quite strict: studies using CBT techniques in a training format without individually tailored case formulation were*	Any control condition	Delusions and auditory hallucinations **Limited to end-of-treatment data*	Clinical Trials Assessment Measure (CTAM)

Author, Year	Objective(s) or Research Question	Search Date and Databases Used	Inclusion Criteria					Method of Quality Assessment
			Study Design	Population	Intervention	Comparator(s)	Outcome(s)	
					only included in sensitivity analyses.			
Velthorst et al, 2015[56]	To investigate the immediate, short- and long-term effectiveness of conventional CBT treatments in reducing negative symptoms	1993 to July 2013 • PsycINFO • PubMed • Cochrane Central Register of Controlled Trials	RCTs	Not explicitly stated	CBT that was targeted at one of the following outcome domains: • Psychotic symptomatology • Negative symptoms • Social functioning • Self-esteem • Cannabis ***and*** CBT intervention contained at least one behavioural (e.g., exposure or activity scheduling) and one cognitive (e.g., challenging dysfunctional beliefs) technique	Not stated	Negative symptom sum score as one of their end-of-treatment outcomes	Clinical Trials Assessment Measure (CTAM)
Wykes et al, 2008[57]	To explore the effect sizes of current CBTp trials including targeted and nontargeted symptoms, modes of action, and effect of methodological rigour	Years searched not specified • Embase • MEDLINE • Current Contents • Web of Science • PsycINFO • Cochrane Collaborative Register of Trials • Hand-searching of meta-analyses and review articles	RCTs	A majority of people with a diagnosis of schizophrenia	CBT as an adjunct to usual care	Any comparator	• Positive symptoms • Negative symptoms • Functioning • Mood • Hopelessness • Social anxiety	Clinical Trials Assessment Measure (CTAM)

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HTA, health technology assessment; MI, motivational interviewing; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial.

Appendix 5: Ongoing Studies Relating to CBT for Psychosis

Table A4: Ongoing Systematic Reviews Related to CBT for Psychosis

ID (Registry)	Title	Review Question(s)
CRD42017060068 (PROSPERO)	For whom is Cognitive Behavioural Therapy (CBT) for psychosis most effective? An IPD meta-analysis of randomised control trials comparing CBT versus standard care and other psychosocial interventions	This evidence synthesis will use IPD meta-analysis to identify the modifiers of treatment response to CBT in patients with schizophrenia-spectrum diagnoses. The treatment modifiers examined will include participants' demographic characteristics (age; gender; ethnicity), participants' clinical characteristics (effect of specific diagnostic groups; illness duration; phase of the illness, e.g., first episode vs. additional episode; duration of untreated psychosis; initial severity of psychotic symptoms; initial severity of comorbid affective symptoms, i.e., anxiety and depression) and specific characteristics of the interventions evaluated in previous and ongoing randomised control trials of CBT for psychosis (number of therapy sessions offered/attended; measures of therapeutic alliance; level of therapists' training and competence; use of manualised interventions; use of individually tailored formulation-based interventions).
CRD42016048403 (PROSPERO)	Treatments for adults with schizophrenia: a systematic review	• What are the benefits and harms of psychosocial and other nonpharmacological treatments for adults with schizophrenia? • How do the benefits and harms of nonpharmacological treatments for adults with schizophrenia vary by patient characteristics*? *Patient characteristics include age, sex, race, ethnicity, socioeconomic status, time since illness onset, prior treatment history, co-occurring psychiatric disorders, pregnancy, etc.
CRD42013003911 (PROSPERO)	Cognitive behavioural therapy for psychosis: a systematic review and meta-analysis	• Is cognitive behavioural therapy (CBT) associated with improvements in overall psychotic symptoms for people with schizophrenia-spectrum diagnoses, when compared to (a) usual treatment and (b) other psychosocial treatments? (PRIMARY OUTCOME) • Is cognitive behavioural therapy (CBT) for people with schizophrenia-spectrum diagnoses associated with increased rates of clinically significant response, when compared to (a) usual treatment and (b) other psychosocial treatments? (PRIMARY OUTCOME) • Is cognitive behavioural therapy (CBT) an acceptable and safe treatment for people with schizophrenia-spectrum diagnoses, when compared to (a) usual treatment and (b) other psychosocial treatments, with consideration of early discontinuation due to adverse effects, suicidality, severe symptom exacerbation, and death? • Is cognitive behavioural therapy (CBT) associated with improvements in functioning (social and vocational) and quality of life for people with schizophrenia-spectrum diagnoses, when compared to (a) usual treatment and (b) other psychosocial treatments? • Is cognitive behavioural therapy (CBT) for people with schizophrenia-spectrum diagnoses associated with reduced rates of relapse (N relapsing, N days in/out of remission / recovery / stability), readmission (time to admission, duration of admission) or deterioration from baseline, when compared to (a) usual treatment and (b) other psychosocial treatments? • Is cognitive behavioural therapy (CBT) for people with schizophrenia-spectrum diagnoses associated with improvement in target symptom (primary outcome of each study), when compared to (a) usual treatment and (b) other psychosocial treatments? • Using meta-regression and sensitivity analysis, what is the effect of treatment duration (weeks and sessions available), blinding (non-blind versus single-blind), publication year, phase of illness (1–2 episodes versus multiple episodes), additional psychosocial treatments (none, minor, moderate and numerous), attrition on overall effect sizes for primary outcomes? • Is cognitive behavioural therapy (CBT) associated with improvements in positive, negative, and general symptoms for people with schizophrenia-spectrum diagnoses, when compared to (a) usual treatment and (b) other psychosocial treatments?
CD009608 (Cochrane)	Cognitive behaviour therapy (group) for schizophrenia	• To investigate the effects of group CBT, compared with: i. standard care; or ii. other psychosocial interventions, for people suffering from schizophrenia

ID (Registry)	Title	Review Question(s)
CD007964 (Cochrane)	Cognitive behaviour therapy versus standard care for schizophrenia	• To assess the effectiveness of adjunct cognitive behavioural therapy for people with schizophrenia compared to standard care alone • To compare the effect the following variables have on outcome: i. people in their first episode of illness with those who have a longer history of illness ii. level of therapist experience and qualification iii. length of treatment/number of sessions

Appendix 6: Results of Applicability and Limitation Checklists for Studies Included in Economic Literature Review

Table A5: Assessment of the Applicability of Studies Assessing the Cost-Effectiveness of CBT for Psychosis

Author, Year	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system in which the study was conducted sufficiently similar to the current Ontario context?	Were the perspectives clearly stated and what were they?	Are estimates of relative treatment effect from the best available source?
Stant et al, 2003, Netherlands[26,67]	Partially, chronic schizophrenia	Yes	No, the Netherlands	Yes, societal	Yes
Haddock et al, 2003, UK[24]	Yes	Partially, dyads with care-givers plus motivational interview	No, UK	Yes, societal	Yes
Barton et al, 2009, UK[23]	Partially, mixed study population with new and recurrent or chronic schizophrenia	Partially, CBTp plus vocational	No, UK	Yes, NHS and PPS	Yes
McCrone et al, 2010, UK[25]	Partially, mixed study population with new and recurrent or chronic schizophrenia	Partially, CBTp within a structured early psychosis intervention	No, UK	Yes, NHS and PPS	Yes
van der Gaag et al, 2011, Netherlands[29]	Partially, chronic schizophrenia	Yes	No, the Netherlands	Yes, societal	Yes
Zhang et al, 2014, China[30]	Partially, stable schizophrenia, < 5 years	Yes, group CBTp only	No, China	Yes, societal	Yes

Author, Year	Are all future costs and outcomes discounted? (If yes, at what rate?)	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgement (directly applicable/partially applicable/ not applicable)
Stant et al, 2003, Netherlands[26,67]	Yes, 4%	No	Yes	Partially applicable
Haddock et al, 2003, UK[24]	Yes, 6%	No	Yes	Partially applicable
Barton et al, 2009, UK[23]	No, 9-month RCT	Yes	Yes	Partially applicable
McCrone et al, 2010, UK[25]	No, 18-month RCT	No	Yes	Partially applicable
van der Gaag et al, 2011, Netherlands[29]	No, 18 month-RCT	No	Yes	Partially applicable
Zhang et al, 2014, China[30]	Yes, 12-month RCT	Yes	Yes	Partially applicable

Abbreviations: CBTp, cognitive behavioural therapy for psychosis; NHS, National Health Service; PPS, Partners Procurement Service; RCT, randomized controlled trial.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

Table A6: Assessment of the Limitations of Studies Assessing the Cost-Effectiveness of CBT for Psychosis

Objective: To assess the cost-effectiveness of CBTp for schizophrenia							
Author, Year	**Does the model structure adequately reflect the nature of the health condition under evaluation?**	**Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?**	**Are all important and relevant health outcomes included?**	**Are the estimates of relative treatment effects obtained from best available sources?**	**Do the estimates of relative treatment effect match the estimates contained in the clinical report?**	**Are all important and relevant (direct) costs included in the analysis?**	**Are the estimates of resource use obtained from best available sources?**
Stant et al, 2003, Netherlands[26,67]	NA	Partially	Yes	Yes	No	Yes	Yes
Haddock et al, 2003, UK[24]	NA	Partially	No	Yes	No	Yes	Yes
Barton et al, 2009, UK[23]	NA	No, 9 months	Yes	Yes	No	Yes	Yes
McCrone et al, 2010, UK[25]	NA	Partially	No	Yes	No	Yes	Yes
van der Gaag et al, 2011, Netherlands[29]	NA	Partially	No	Yes	No	Yes	Yes
Zhang et al, 2014, China[30]	NA	No, 12 months	Yes	Partially, not clear about calculation of QALY estimates	No	Yes	Yes

Author, Year	**Are the unit costs of resources obtained from best available resources?**	**Is an appropriate incremental analysis presented or can it be calculated from the reported data?**	**Are all important and uncertain parameters subjected to appropriate sensitivity analysis?**	**Is there a potential conflict of interest?**	**Overall assessment including applicability to the project (Minor limitations/ potentially serious limitations/very serious limitations)**
Stant et al, 2003, Netherlands[26,67]	Yes	No	No	Unclear	Potentially serious limitations
Haddock et al, 2003, UK[24]	Yes	Yes	Partially	Unclear	Potentially serious limitations
Barton et al, 2009, UK[23]	Yes	Yes	Yes	Unclear	Minor limitations
McCrone et al, 2010, UK[25]	Yes	Yes	Partially	Unclear	Potentially serious limitations
van der Gaag et al, 2011, Netherlands[29]	Yes	Yes	Yes	Unclear	Minor limitations
Zhang et al, 2014, China[30]	Yes	Partially, could not recalculate mean costs	No	Unclear	Potentially serious limitations

Abbreviations: CBT, cognitive behavioural therapy; NA, not applicable, QALY, quality-adjusted life years.
Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

Appendix 7: Cost-Effectiveness Analysis: Results

Table A7: Cost-Effectiveness Analysis, Sequential Approach: CBT for Psychosis Compared With Usual Care, Cost per Life-Year Saved

Strategy	Mean Costs, $[a] (95% CrI)	Mean LYs (95% CrI)	Incremental Costs,[b] $ (95% CrI)	Incremental LYs[c] (95% CrI)	ICER: $/LY Saved
Usual care	90,294.95 (88,126–92,496)	4.527 (4.48–4.56)			
CBT for psychosis by nonphysician	92,789.30 (90,669–94,958)	4.542 (4.50–4.58)	2,494.35 (1,472–3,544)	0.0157 (−0.00 to 0.04)[d]	158,656
CBT for psychosis by physician	95,765.44 (93,657–97,981)	4.542 (4.50–4.58)	2,976.15 (2,822–3,129)	0.00	Dominated

Abbreviations: CBT, cognitive behavioural therapy; CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

[a]All costs in 2017 Canadian dollars. All costs and effects were discounted at 1.5%.

[b]Incremental cost = mean cost (CBT for psychosis strategy) − mean cost (usual care).

[c]Incremental effect = mean effect (CBT for psychosis strategy) − mean effect (usual care).

[d]95% CrI −0.0003 to 0.036.

Note: Results may appear inexact because of rounding.

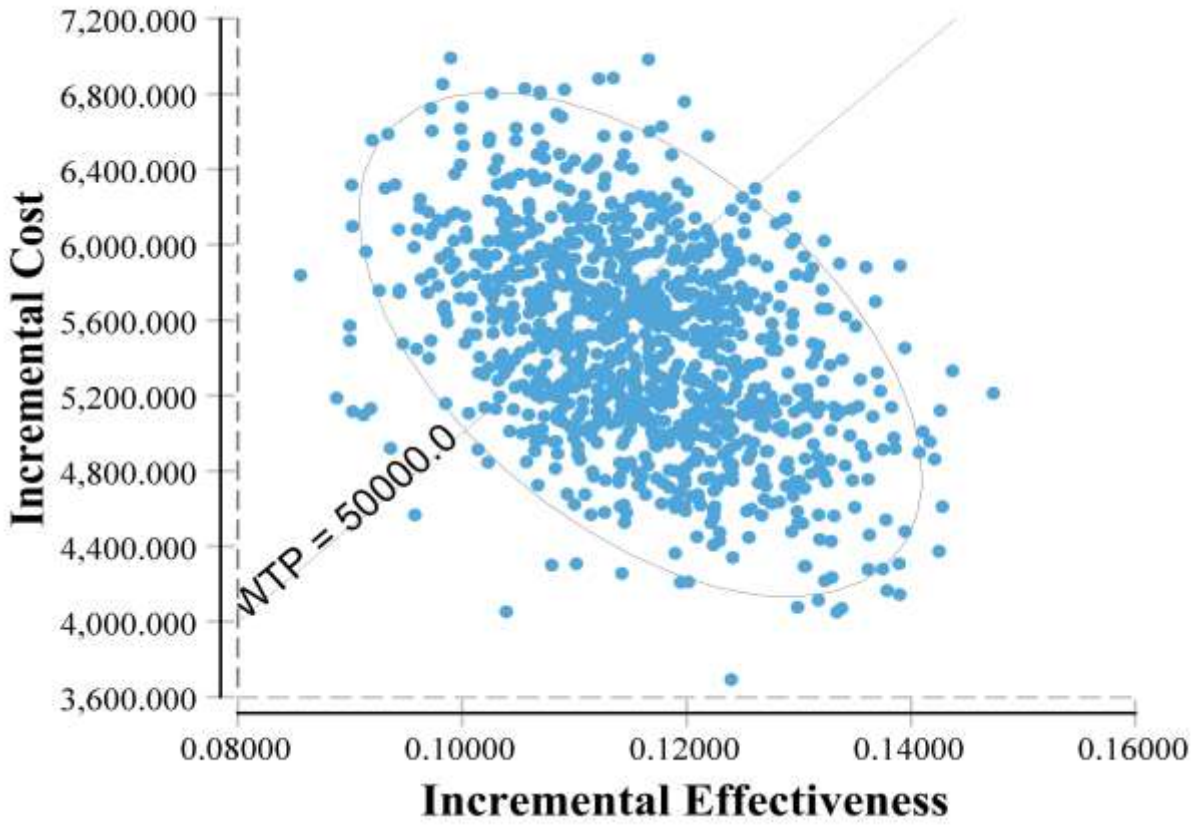

Figure A1: Scatter Plot of 1,000 Simulated Pairs of Incremental Costs and Effects in the Cost-Effectiveness Plane: CBT for Psychosis by Physicians vs. Usual Care

Abbreviations: CBT, cognitive behavioural therapy; WTP, willingness-to-pay threshold.
All costs are in 2017 Canadian dollars and discounted at 1.5%. Effectiveness is expressed in quality-adjusted life-years (QALYs). The diagonal line indicates a willingness-to-pay threshold of $50,000 per QALY gained. The incremental cost-effectiveness ratio ($47,196/QALY gained) is the slope of a straight line from the origin that passes through the (0.012 QALY, $5,470) coordinate. A 95% confidence ellipse covers 95% of the estimated joint density and was used to represent uncertainty around the incremental cost-effectiveness ratio estimated in the probabilistic sensitivity analysis.

Appendix 8: Letter of Information

Letter of Information

Health Quality Ontario is conducting a review of **Cognitive Behavioural Therapy for Psychosis** due to Schizophrenia. The purpose is to understand whether this therapy should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and caregivers of those who have experience with psychosis due to schizophrenia, and who may or may not have received cognitive behavioural therapy. Our goal is to make sure the experiences of patients and caregivers are considered in the funding recommendations for Cognitive Behavioural Therapy for Psychosis.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-50 minutes of your time for a phone or in-person interview
- ✓ Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 30-50 minutes. It will be held in a private location or over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

Risks to participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

If you are interested, please contact

Appendix 9: Interview Guide

CANDIDATE:	INTERVIEWER:	DATE:
Overview – What is Health Quality Ontario's mandate? What is Health Technology Assessment? Health Quality Ontario (HQO) is a provincial agency dedicated to ensuring our health care system delivers a better experience of care and better outcomes for Ontarians at better value for money. Part of this role includes evaluating the effectiveness of health care technologies and services through a process called health technology assessment. Health Technology Assessment projects involve rigorous clinical and economic evidence review on the effective, safety, and cost of technologies while considering the perspectives of patients and caregivers who have experience with the particular condition or technology in question. We are currently reviewing **cognitive behavioural therapy**. I am calling you to hear about your experience with **your condition** and the treatment options available.		
QUESTION 1: If it is okay with you, please share how and when you were diagnosed with psychosis? **How do psychotic episodes impact your day-to-day routine? How would you describe your quality of life?** *(e.g., emotional/psychological effects, fatigue, stress, depression, physical challenges, financial, inability to work or go to school, etc.)* ***If Caregiver**, What is it like to care for someone with psychosis? What is your day-to-day routine? How would you describe your quality of life?*		
CANDIDATE RESPONSE:		
QUESTION 2: What treatments are accessible to you and which are the ones you have explored? How are currently available treatments meeting your needs? What needs are unaddressed? *(What other therapies are they aware of? Which ones are accessible to them? How are these helpful to them in terms of addressing the challenges and what are the most important benefits?* *What are their unmet needs from these treatments? What is the positive and negative impact of currently available treatment, what are the side-effects of currently available treatments and are these tolerable?)*		
CANDIDATE RESPONSE:		

QUESTION 3a.: For those people who did not use CBT or who had tried both standard treatment and the treatment under evaluation:

What treatment do you have preference for?

If prefer CBT, what challenges would CBT access address?

(Is there a long journey through many health care providers? Are there financial burden not supported by health insurance? Travel required for technology? Accessible? Repeat visits, uncomfortable/painful procedure, Embarrassing? Time off work/school? Are there other choices available?)

Are there any other benefits you see to this treatment being available? What are the most important things you would like to gain from CBT?

(Does it offer effective treatment? Better access or easier use? Is it more effective or safer? Control of condition or symptoms? Less intrusive or painful, future benefits, better quality of life, ability to go about your daily life, improve experience?)

CANDIDATE RESPONSE:

QUESTION 3b.: For those people with experience of using CBT, which type did they try?

1. Low-intensity/brief CBT (Length of CBT received?)
2. Physician service provider versus nonphysician service provider
3. Individual versus group therapy
4. Online CBT for psychosis

What difference did it make to your quality of life?

What was the impact of having treatment: *Treatment changes, quality of life change, empowerment and ownership of condition, improvement in adherence to treatment, lifestyle change, more tests after the first test, invasiveness, fewer tests, consequences of treatment, financial burden, other health care services)*

What was the impact of having/taking the treatment*: (Anxiety before/after, pain, side effects, embarrassment, time off work/school etc)*

If paid by the patient: *(new treatment easy or more difficult, easy to understand, is daily life less impeded, what is the financial impact on family and patients)*

Have people actually gained what was important to them with the new treatment? *Did the new treatment meet expectations?*

CANDIDATE RESPONSE:

- ***The biggest challenges of living with psychosis are*** *…* _____
- ***Other treatments are adequate/inadequate because*** *…* _____
- ***CBT being assessed will be/will not be beneficial because*** *…* _____

Thank you for sharing your story and your insights on this condition and the available technologies. We will use these insights to draft our report and recommendation for funding. The draft report will be posted on our public website for comments, and we would welcome you to review and share your thoughts on it. If you wish, we could email you to alert you about this posting.

If we do not have their email, request it and add to the stakeholder list _____

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About Health Quality Ontario

Health Quality Ontario is the provincial lead on the quality of health care. We help nurses, doctors and others working hard on the frontlines be more effective in what they do – by providing objective advice and by supporting them and government in improving health care for the people of Ontario.

Our focus is making health care more effective, efficient and affordable which we do through a legislative mandate of:

- Reporting to the public, organizations and health care providers on how the health system is performing,
- Finding the best evidence of what works, and
- Translating this evidence into concrete standards, recommendations and tools that health care providers can easily put into practice to make improvements.

Health Quality Ontario is governed by a 12-member Board of Directors appointed by the Minister of Health and Long-Term Care and with representation from the medical and nursing professions, patients and other segments of health care.

In everything it does, Health Quality Ontario brings together those with first-hand experience – doctors, nurses, other health care providers, patients and families – to hear their experiences and how to make them better. Health Quality Ontario also works collaboratively with organizations across the province to encourage the spread of innovative and proven programs to support high quality, while also saving money and eliminating redundancy. And, we partner with patients to be full participants in designing our programs – another part of our work we take very seriously.

Examples of what we do include providing ways for clinicians to use their collective wisdom and experience to bring about positive change. In 2017, 29 Ontario hospitals participated in a pilot program that reduced infections due to surgery by 18%. This program enabled surgeons to see their surgical data and how they perform in relation to each other and to 700 other hospitals worldwide. We then helped them identify and action improvement practices. Forty-six hospitals across Ontario are now part of this program.

We also develop quality standards that are based on the best evidence, to guide on caring for health conditions where there are gaps in care. Each quality standard provides recommendations to government, organizations and clinicians, and is accompanied by a guide for patients to help them ask informed questions about their care.

In addition, Health Quality Ontario's health technology assessments use evidence to assess the value for money and safety of new technologies and procedures and make recommendations to government on whether or not they should be funded.

And each year, we help organizations across the system create Quality Improvement Plans, for improving health care quality.

Health Quality Ontario is committed to supporting the development of a quality health care system based on six fundamental dimensions: efficient, timely, safe, effective, patient-centred and equitable.

Our goal is to challenge the status quo and to focus on long-lasting pragmatic solutions that improve the health of Ontarians, enhance their experience of care, reduce health care costs, and support the well-being of health care providers – because we believe a quality health system results in Ontarians leading healthier and more productive lives, and a vibrant society in which everyone benefits.

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ISSN 1915-7398 (online)
ISBN 978-1-4868-2368-0 (PDF)