UNIVERSIDADE DE SOROCABA
PRÓ-REITORIA DE PÓS-GRADUAÇÃO, PESQUISA, EXTENSÃO E INOVAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS

MAÍRA RAMOS ALVES

AVALIAÇÃO CRÍTICA E COMPARAÇÃO DE RECOMENDAÇÕES DE DIRETRIZES DE PRÁTICA CLÍNICA PARA O TRATAMENTO DA ESQUIZOFRENIA EM CRIANÇAS E ADOLESCENTES:
UMA PESQUISA METODOLÓGICA

CRITICAL APPRAISAL AND COMPARISON OF RECOMMENDATIONS OF CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF SCHIZOPHRENIA IN CHILDREN AND ADOLESCENTS:
A METHODOLOGICAL SURVEY

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Mestre em Ciências Farmacêuticas.

Orientadora: Profa. Dra. Luciane Cruz Lopes

Sorocaba/SP
2022

Ficha Catalográfica

Alves, Maíra Ramos

A48a Avaliação crítica e comparação de recomendações de diretrizes de prática clínica para o tratamento da esquizofrenia em crianças e adolescentes : uma pesquisa metodológica = Critical appraisal and comparison of recommendations of clinical practice guidelines for the treatment of schizophrenia in children and adolescents : a methodological survey / Maíra Ramos Alves. – 2022.

63 f. : il.

Orientadora: Profa. Dra. Luciane Cruz Lopes

Dissertação (Mestrado em Ciências Farmacêuticas) – Universidade de Sorocaba, Sorocaba, SP, 2022.

1. Esquizofrenia. 2. Esquizofrenia nas crianças - Tratamento. 3. Esquizofrenia em adolescentes – Tratamento. 4. Diretrizes para a prática clínica. I. Lopes, Luciane Cruz, orient. II. Universidade de Sorocaba. III. Título.

Elaborada por Regina Célia Ferreira Boaventura – CRB-8/6179

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Aprovado em: 13/12/2021

BANCA EXAMINADORA:

Profa. Dra. Luciane Cruz Lopes
Universidade de Sorocaba

Prof. Dr. Airton Tetelbom Stein
Universidade Federal de Ciências da Saúde de Porto Alegre

Profa. Dra. Ávila Teixeira Vidal
Ministério da Saúde

Aos meus pais, meus maiores incentivadores.

AGRADECIMENTOS

Agradeço primeiramente aos meus pais pelo amor e dedicação que sempre tiveram comigo. Obrigada por me ensinarem a seguir sempre em frente e me fazerem ter fé em mim mesma. Sem vocês este sonho não seria possível.

A minha família, que torceu por mim e esteve ao meu lado mesmo quando eu não conseguia estar com eles.

A minha orientadora, Luciane Cruz Lopes, pela dedicação, orientação e por acreditar no meu potencial quando eu mesma duvidei. Você foi fundamental no meu crescimento acadêmico e pessoal e eu jamais esquecerei de seus ensinamentos.

Aos professores Silvio Barberato-Filho, Cristiane Bergamaschi e Daniela Melo, e aos colegas Jardel Oliveira, Flávia Blaseck e Franciele Cordeiro pelas contribuições, apoio e aprendizados. Este projeto não teria sido o mesmo sem vocês.

A Rejane Mayer, que fez parte desta jornada desde o início e a quem sou muito grata pela amizade e parceria. Obrigada por fazer parte de mais esse capítulo.

A Fabiane Motter, pela disponibilidade, apoio e amizade. Nossa parceria tornou possível coisas incríveis nesta jornada.

A todos os professores, colegas e funcionários do Programa de Pós-graduação em Ciências Farmacêuticas da Universidade de Sorocaba. Meu muito obrigada à cada um que passou por mim, me ensinou algo, me apoiou, seja qual tenha sido a forma, durante todo esse período.

Não considere nenhuma prática como imutável. Mude e esteja pronto a mudar novamente. Não aceite verdade eterna. Experimente.

(B. F. Skinner)

RESUMO

Introdução: O número de diretrizes de prática clínica (CPG) tem aumentado substancialmente, principalmente na área da saúde mental pediátrica. No entanto, pouco se sabe sobre a qualidade das diretrizes de prática clínica e das recomendações para o tratamento de transtornos como a esquizofrenia em crianças e adolescentes. **Objetivo:** Avaliar a qualidade do reporte das diretrizes e das recomendações para o tratamento e manejo da esquizofrenia em crianças e adolescentes. **Métodos:** As diretrizes de prática clínica foram identificadas por meio de um protocolo prospectivo de busca sistemática no EMBASE (Excerpta Medical Database, via Ovid); MEDLINE (via Ovid); PsycINFO (via Ovid); PubMed, Epistemonikos; Biblioteca Virtual em Saúde; Global Index Medicus e bancos de dados específicos para diretrizes clínicas. Foram considerados para inclusão documentos de 2004 a dezembro de 2020. A qualidade das diretrizes foi avaliada de forma independente por três ou quatro revisores usando os instrumentos AGREE II. As diretrizes foram consideradas de alta qualidade se pontuaram ≥60% nos domínios 3 e 6 do instrumento AGREE II. Os diferentes sistemas de classificação de evidências foram descritos, a qualidade das recomendações foi avaliada em pares utilizando o instrumento AGREE-REX e as recomendações foram descritas e comparadas. **Resultados:** A busca nas bases de dados recuperou 3.182 resultados. Destes, 2.030 foram selecionados e 29 seguiram para a etapa de leitura de texto completo. Após esta fase, 4 diretrizes foram selecionadas para extração. Apenas uma das diretrizes foi considerada de alta qualidade na avaliação usando o AGREE II. As recomendações farmacológicas foram as únicas descritas para todas as fases do tratamento. As pontuações do AGREE-REX foram menores para as recomendações psicossociais. **Conclusão:** Ainda são poucos os estudos clínicos e as diretrizes sobre esquizofrenia em crianças e adolescentes. A qualidade dos documentos era geralmente baixa e a qualidade do reporte das recomendações tem muito a melhorar. Também falta transparência acerca da qualidade das evidências e força das recomendações.

Registro do Protocolo: PROSPERO - CRD42020164899

Palavras-chave: Diretrizes de Prática Clínica; Crianças; Esquizofrenia.

ABSTRACT

Introduction: The number of clinical practice guidelines (CPG) has increased substantially, mainly in the pediatric area of mental health. However, little is known about the quality of the CPG and of the recommendations for treating diseases such as schizophrenia in children and adolescents. **Objective:** To assess the quality of the report of guidelines and the recommendations for the treatment and management of schizophrenia in children and adolescents. **Methods:** Clinical practice guidelines were identified using a prospective protocol for systematic search on EMBASE (Excerpta Medical Database, via Ovid); MEDLINE (via Ovid); PsycINFO (via Ovid); PubMed, Epistemonikos; Biblioteca Virtual em Saúde; Global Index Medicus, and specific databases for clinical guidelines. Were considered for inclusion documents from 2004 to December 2020. The quality of the guidelines was independently assessed by three or four reviewers using the AGREE II instruments. Guidelines were considered of high quality if they score ≥60% in domains 3 and 6 of the AGREE II instrument. The different evidence classification systems were described, the quality of recommendations was assessed in pairs using the AGREE-REX instrument, and the recommendations were described and compared. **Results:** The search in the databases retrieved 3,182 results. Of these, 2030 were screened and 29 were selected for full-text reading. After this phase, 4 guidelines were selected for extraction. Only one of the CPG was considered of high quality in the AGREE II assessment. The pharmacological recommendations were the only ones described for all treatment phases. Scores of AGREE-REX were lower for psychosocial recommendations. **Conclusion:** There are still few clinical studies and CPG regarding schizophrenia in children and adolescents. The quality of the documents was overall low, and the quality of the recommendations report has much to improve. There is also a lack of transparency about the quality of the evidence and the strength of the recommendations.

Protocol Registration: PROSPERO - CRD42020164899

Keywords: Clinical Practice Guidelines. Children. Schizophrenia.

LISTA DE ILUSTRAÇÕES

LISTA DE SIGLAS E ABREVIATURAS

AGREE	Appraisal of Guidelines for Research & Evaluation
AGREE-REX	Appraisal of Guidelines for Research & Evaluation Recommendation Excellence
COI	Conflict of Interest
CPG	Clinical Practice Guidelines
DSM	Diagnostic and Statistical Manual of Mental Disorders
GDG	Guideline Development Group
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
ICC	Intra-class Correlation Coefficients
IOM	US Institute of Medicine
IQR	Interquartile Range
NICE	National Institute for Health and Care Excellence
PICAR	Population & clinical indication(s), Intervention(s), Comparator(s), Attributes of CPG, Recommendation characteristics
PICO	Population, Intervention(s), Comparator(s), and Outcome(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO	International Prospective Register of Systematic Reviews
SD	Standard Deviation

SUMÁRIO

1 INTRODUCTION

The schizophrenia spectrum includes many disorders with at least one of the following symptoms: delusions, hallucinations, disorganized thinking/speech, disorganized or abnormal motor behavior, and negative symptoms [1]. It is believed that genetic factors can explain around 80% of the risk of development of the disorder, but the interaction of these with environmental factors can also influence the onset of the disorder [2]. Its onset predominantly occurs in adolescence and early adulthood, being most prevalent in individuals around 40 years of age [3].

Onsets in childhood are extremely rare, occurring in less than 1% of the cases despite the high prevalence of psychotic symptoms in healthy children [4, 5]. The earlier the onset, the more severe is the course of the disorder, with a higher incidence of deficits, negative symptoms, and autistic traits [6]. Due to this significant impact on the development of the child, the treatment must start as soon as possible, always combining psychopharmacological, psychological, and psychosocial therapies [4]. Also, because treatment impacts so much on the patient's prognosis, the quality of the guidance provided for health professionals is important.

Identifying the highest quality guidelines is key to tracking and implementing recommendations that are trustworthy and will provide more benefits than harms to schizophrenia patients [7, 8]. Many instruments have been created to assess the quality of guidelines, one of them being the Appraisal of Guidelines for Research & Evaluation (AGREE) II, developed in 2003 and updated to the current version in 2009 [8-10]. Another important instrument that assesses the quality of the recommendations within the guidelines is the AGREE-REX, created in 2019 as a complement to the AGREE II assessment [11].

During our preliminary searches, no guideline quality assessment targeting guidelines for schizophrenia in children and adolescents was found. Although the criteria for diagnosis of schizophrenia is the same for adults and children since the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), some treatments used by adults cannot or still have gaps in evidence to be used in children, making guidelines specific for this population necessary [4, 12, 13]. For the same reasons, the quality of the already existing guidelines and their recommendations should be clear, both to help guide the choice for the best guidance by health professionals and to inform future panelists about what has been made in the past years and can be achieved or better up by them.

2 THEORETICAL FRAMEWORK

2.1 Schizophrenia in children and adolescents

The incidence of schizophrenia in children is rare, becoming more prevalent as adolescence advances [12, 14]. It is estimated that early onsets occur in between 0.03% and 0.04% of the population, one-fifth of those being very-early onsets, even though the rarity of the incidence makes epidemiological estimates very difficult and imprecise [4, 15, 16].

In the premorbid phase, children usually present developmental problems that affect language, social skills, motricity, behavior, learning, memory, and attention [15, 17]. Teenagers can present other disorders such as anxiety, depression, and disturbing behavior [18, 19]. In this phase, psychosocial functioning is usually poor within this population, which can be understood as a risk factor for the development of the disorder, such as family history, psychiatric and health problems, and childhood trauma [18, 20].

The first signs and symptoms start to appear in the prodromal phase [12]. They can appear in the form of a retraction, bizarre behavior, magic and bizarre thoughts, impairments in speech and learning, and dullness in affect and initiative [17]. The most common clinical manifestations in this phase are verbal and auditory hallucinations and perceptive delusions [14, 20].

In the acute phase, there is a difference between very-early-onsets and early-onsets. In the more precocious group, there is a higher incidence of negative symptoms before the positive symptoms arise, which usually compromises, even more, the development of the individual, leading to worse prognostics [21]. In teenagers, however, positive symptoms are the first to show off, usually in an aggressive form [17]. They can also show some deficits in fine motor skills, probably due to the impairments in neurological development present in patients with schizophrenia [22].

In schizophrenia, independently of the patient's age, the diagnostic process is predominantly clinical [23]. Clinicians must discard any organic cause, make a detailed physical and neurological examination in the patient, use rating scales whenever they find necessary, and make sure that rare conditions and frequently misdiagnoses have been considered [4]. The possible clinical conditions that could result in a psychotic state, or a diagnosis of affective psychosis or neurodevelopmental disorder, such as autism, should be extensively searched and discarded to confirm the diagnosis of schizophrenia [12, 17]. Differential diagnosis is especially complex in such cases [5]. There should be an attentive

observation in the marks of development of the child, to the report of signs and symptoms typical of the disorder, such as delusions and hallucinations and the age of first symptoms [12, 24, 25].

Common comorbidities are obsessive-compulsive disorder, attention deficit, and hyperactivity disorder, neurocognitive disorders, and mood disorders [4]. These can affect diagnosis as well since there is a difficulty in distinguishing premorbid schizophrenia signs and symptoms of possible comorbidities symptoms [24].

Stigma is a well-known difficulty faced by people with schizophrenia and children and teenagers are also affected by it [26, 27]. It is defined as a deeply discrediting attribute associated with a given condition that leads to a perception of social inferiority and consists of three main components: stereotypes, prejudice, and discrimination [26]. It can affect the diagnostic process, social skills, quality of life, and adherence to the treatment [28, 29]. Interventions to reduce the stigma are important to people living with mental disorders in general; however, the evidence supporting the existing interventions is still modest [30].

The gold standard treatment for schizophrenia in the young population is the combination of psychosocial/psychological and psychopharmacological interventions [5]. Cognitive remediation therapy and cognitive behavioral therapy showed good results on the improvement of cognitive and social aspects, respectively, in children and adolescents with schizophrenia [31]. For medication, Clozapine is described as the most efficacious among the other antipsychotics for youngsters [13]. However, we still lack information about the monitoring of adverse effects related to the on- and off-label use of antipsychotics by children and adolescents, which should be addressed while recommending this class of medication to this population [32-34].

Public policies addressing children and adolescents' mental health are not a reality in most countries according to the World Health Organization Mental Health Atlas 2017 [35]. However, the creation of specific policies for this population is recommended to better guide the mental health services offered for them [36]. Part of the construction of these health policies involves the implementation of well-developed, well-reported, evidence-based clinical practice guidelines (CPG) into the services [37].

2.2 Clinical Practice Guidelines

Following the definition given by the US Institute of Medicine (IOM) in 2011, CPGs "are statements that include recommendations intended to optimize patient care that is informed

by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [38]. The production of this kind of documents increased since the late 1970s in all health areas, to attend to a demand of the health care systems for improvements in patient care [37]. They differ from other documents compiling clinical recommendations, such as practice standards and consensus statements, for their systematic approach and method for development [39].

There have been some attempts to standardize the development of guidelines in the past years [39, 40]. One of the most famous standards developed until now that explain the fundamental steps for guideline development are the ones by the IOM [38], described in **Table 1**.

Table 1 – US Institute of Medicine standards for trustworthy clinical practice guidelines

Guideline Standards	Definition
1. Establishing Transparency	The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible.
2. Management of Conflict of Interest (COI)	1. Prior to selection of the guideline development group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG: • Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), noncommercial, intellectual, institutional, and patient–public activities pertinent to the potential scope of the CPG. 2. Disclosure of COIs within GDG: • All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of his or her work. • Each panel member should explain how his or her COI could influence the CPG development process or specific recommendations. 3. Divestment: • Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations. 4. Exclusions • Whenever possible GDG members should not have COI. • In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG. • Members with COIs should represent not more than a minority of the GDG. • The chair or co-chairs should not be a person(s) with COI. • Funders should have no role in CPG development.

3. Guideline Development Group Composition	1. The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG. 2. Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient, and a patient advocate or patient/consumer organization representative in the GDG. 3. Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.
4. Clinical Practice Guideline–Systematic Review Intersection	1. Clinical practice guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. 2. When systematic reviews are conducted specifically to inform particular guidelines, the GDG and systematic review team should interact regarding the scope, approach, and output of both processes.
4. Establishing Evidence Foundations for and Rating Strength of Recommendations	1. For each recommendation, the following should be provided: • An explanation of the reasoning underlying the recommendation, including o A clear description of potential benefits and harms o A summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence o An explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation • A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation • A rating of the strength of the recommendation in light of the preceding bullets A description and explanation of any differences of opinion regarding the recommendation
5. Articulation of Recommendations	1. Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed. Strong recommendations should be worded so that compliance with the recommendation(s) can be evaluated.
6. External Review	1. External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public. 2. The authorship of external reviews submitted by individuals and/or organizations should be kept confidential unless that protection has been waived by the reviewer(s). 3. The GDG should consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments. A draft of the CPG at the external review stage or immediately following it (i.e., prior to the final draft) should be made available to the general public for comment. Reasonable notice of impending publication should be provided to interested public stakeholders.
7. Updating	1. The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG. 2. Literature should be monitored regularly following CPG publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the CPG. CPG should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations.

Adapted from: Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington D.C.: National Academies Press; 2011.

After these standards, new challenges in the development of those documents have arisen. One of them is the overwhelming quantity of guidelines that are, in many cases, addressing the same recommendations or are conflicting [41-43]. The reasons for that may vary but some are already known, such as the bad reporting of the management of conflicts of interest, biased selection of panelists, and no reporting of gaps and instructions for future panelists [42, 44, 45].

These problems in the development and reporting process can also affect the implementation of the CPG, one of the most challenging aspects of creating such documents [37]. While selecting the evidence and transforming them into recommendations requires a rigorous methodological process to avoid biases [46], the implementation may require the incentive of behavioral changes from clinicians and a careful look to dissemination practices [37, 43, 45].

Both these processes, behavioral change, and dissemination, can be achieved using strategies such as recognizing the profile of the clinicians, their levels of readiness to change, the knowledge gap between them and the evidence and other psychosocial aspects that can help in the knowledge translation process [43, 45]. Also, there should be an investment in implementation strategies throughout all health sectors aligned with prioritization, stakeholders' involvement, cultural adaptations, and monitoring [37].

Systematic assessments of CPG also can help address the knowledge gaps in these documents [47]. In this study design, the use of guideline appraisal instruments is common and, although many instruments have been created in the past years, one of the most used is the AGREE II tool [8, 46, 47], which will be addressed in the following section.

2.3 AGREE Tools

The first version of the AGREE instrument was created in 2003 by an international collaboration of researchers as a tool to assess the quality of CPG [48, 49]. Later in 2009, the instrument was updated to the AGREE II version and, since then, the 23-items instrument, divided into six domains and rated in Likert scale (**Table 2**) has become the first choice of guideline appraisers worldwide [8, 48].

The development of such an instrument was born out of the great variability in the quality of the CPG, in a sense of facilitating the development and report of these documents [7, 10]. It is a broad instrument that can be applied to preventive, diagnostic, or therapeutic CPG of any health condition [46, 48].

Table 2 - Components of the AGREE II instrument

Domains	Items	
1. Scope and Purpose	1.	The overall objective(s) of the guideline is (are) specifically described.
	2.	The health question(s) covered by the guideline is (are) specifically described.
	3.	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
2. Stakeholder Involvement	4.	The guideline development group includes individuals from all relevant professional groups.
	5.	The views and preferences of the target population (patients, public, etc.) have been sought.
	6.	The target users of the guideline are clearly defined.
3. Rigour of Development	7.	Systematic methods were used to search for evidence.
	8.	The criteria for selecting the evidence are clearly described.
	9.	The strengths and limitations of the body of evidence are clearly described.
	10.	The methods for formulating the recommendations are clearly described.
	11.	The health benefits, side effects, and risks have been considered in formulating the recommendations.
	12.	There is an explicit link between the recommendations and the supporting evidence.
	13.	The guideline has been externally reviewed by experts prior to its publication.
	14.	A procedure for updating the guideline is provided.
4. Clarity of Presentation	15.	The recommendations are specific and unambiguous.
	16.	The different options for management of the condition or health issue are clearly presented.
	17.	Key recommendations are easily identifiable.
5. Applicability	18.	The guideline describes facilitators and barriers to its application.
	19.	The guideline provides advice and/or tools on how the recommendations can be put into practice.
	20.	The potential resource implications of applying the recommendations have been considered.
	21.	The guideline presents monitoring and/or auditing criteria.
6. Editorial Independence	22.	The views of the funding body have not influenced the content of the guideline.
	23.	Competing interests of guideline development group members have been recorded and addressed.

Adapted from: AGREE Next Steps Consortium. The AGREE II Instrument 2017. Available from: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf.

Following the creation of the AGREE II instrument, the AGREE Consortium has already launched additional tools to help researchers in the guideline appraising process [50]. One of the most recent ones is AGREE Recommendation Excellence (AGREE-REX), created

in 2019 to help the implementability, applicability, and quality of recommendations in response to studies that demonstrated that high-quality CPG development processes could not guarantee individual recommendations credibility and implementability [50-52].

The instrument has nine items, divided into three domains (**Table 3**) and, as seen in the AGREE II instrument, is rated using a 7-point Likert scale [11]. In a recent study [51, 52], in which 161 CPG were appraised using AGREE-REX, the tool showed great potential in becoming a guiding tool to the development and reporting of high-quality recommendations [52].

Table 3 - Components of the AGREE-REX instrument

Domains	**Items**
Clinical Applicability	1. Evidence
	2. Applicability to Target Users
	3. Applicability to Patients/Populations
Values and Preferences	4. Values and Preferences of Target Users
	5. Values and Preferences of Patients/Populations
	6. Values and Preferences of Policy/Decision-Makers
	7. Values and Preferences of Guideline Developers
Implementability	8. Purpose
	9. Local Application and Adoption

Adapted from: AGREE-REX Research Team. The Appraisal of Guidelines Research & Evaluation—Recommendation EXcellence (AGREE-REX) 2019. Available from: https://www.agreetrust.org/wp-content/uploads/2019/04/AGREE-REX-2019.pdf.

AGREE-REX is a complement to AGREE II and their use in combination is recommended to support evaluation goals [11]. The developers believed that the use of both tools can help diminish the difficulties in the recommendations' implementation and context adaptation of the CPG [52]. The user's manual does not specify the order of appliance, leaving some suggestions of it only for when the assessment involves prioritization/hierarchization of the selected CPG [11].

3 OBJECTIVES

To assess the quality of the guidelines and the recommendations for the treatment and management of schizophrenia in children and adolescents.

3.1 Secondary objectives

a) To evaluate the quality of the guidelines selected using the AGREE II tool.
b) To evaluate the quality of the recommendations contained in them using AGREE-REX.
c) To compare the recommendations and interventions described in the guidelines.

4 RESULTS

The results of the present study were presented in a scientific paper entitled "Critical appraisal and comparison of recommendations of clinical practice guidelines for the treatment of schizophrenia in children and adolescents: a methodological survey" following the recommendations of the University of Sorocaba's Graduate Course in Pharmaceutical Sciences (**Appendix 1**). The paper, which was submitted to an Open Access journal and is now being processed, was presented as follows.

Critical appraisal and comparison of recommendations of clinical practice guidelines for the treatment of schizophrenia in children and adolescents: A methodological survey

Maíra Ramos Alves[1], Cristiane de Cássia Bergamaschi[1], Silvio Barberato-Filho[1], Daniela Oliveira de Melo[2], Rejane Coan Ferretti Mayer[1], Franciele Gabriel Cordeiro[3], Nigar Sekercioglu[4], Flávia Blaseck Sorrilha[1], Carmen Verônica Mendes Abdala[5], Luciane Cruz Lopes[1]*

[1]Graduate Course in Pharmaceutical Sciences, University of Sorocaba, Sorocaba, São Paulo, Brazil

[2]Graduate Course in Pharmaceutical Sciences, Federal University of São Paulo, São Paulo, São Paulo, Brazil

[3]Graduate Course in Drugs and Medicines, University of São Paulo, São Paulo, São Paulo, Brazil

[4]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

[5]Latin American and Caribbean Center on Health Sciences Information, Pan American Health Organization / World Health Organization, São Paulo, São Paulo, Brazil

*Corresponding author
Graduate Course in Pharmaceutical Sciences, University of Sorocaba, UNISO, Brazil
Rodovia Raposo Tavares, KM 92,5 - Sorocaba, São Paulo, Brazil
ZIP Code: 18023-000
Phone: 55 19 99781-8441 Fax: 55 15 2101-7074
Email: luciane.lopes@prof.uniso.br; luslopesbr@gmail.com

Declarations of interest: none.

Abstract

Introduction: The production of clinical practice guidelines (CPG) has grown in the past years. Notwithstanding, the quality of these documents and their recommendations for the treatment of schizophrenia in children and adolescents is still unknown. **Objective:** To assess the quality of the guidelines and recommendations for the treatment of schizophrenia in children and adolescents. **Methods:** CPG were identified through a systematic search on EMBASE; MEDLINE; PsycINFO; PubMed, Epistemonikos; Biblioteca Virtual em Saúde; Global Index Medicus, and specific CPG databases. We considered for inclusion documents from 2004 to December 2020. The CPG quality was independently assessed by three reviewers using AGREE II. CPG were considered of high quality if they scored ≥60% in domains 3 and 6 of AGREE II. The evidence classification systems were described, the quality of recommendations was assessed in pairs using AGREE-REX, and the recommendations were described and compared. **Results:** The databases search retrieved 3,182 results; 2030 were screened and 29 were selected for full-text reading. Four guidelines were selected for extraction. Two CPG were considered of high quality in the AGREE II assessment. The pharmacological recommendations were the only ones described in all treatment phases. Scores of AGREE-REX were lower for psychosocial recommendations. **Conclusion:** There are still few clinical studies and CPG regarding schizophrenia in children and adolescents. The quality of the documents was overall low, and the quality of the recommendations report has much to improve. There is also a lack of transparency about the quality of the evidence and the strength of the recommendations.

Protocol Registration: PROSPERO - CRD42020164899

Keywords: Clinical Practice Guidelines. Children. Schizophrenia.

1 Introduction

Schizophrenia is a chronic mental disorder with a low prevalence, and its precocious form is rare and debilitating (Charlson et al., 2018; Da Fonseca and Fourneret, 2018). Epidemiological studies about early and very early-onset schizophrenia (EOS and VEOS) are also rare, due to the late identification of the disorder and to historic events (Da Fonseca, 2009). In the 1970s, neurodevelopmental disorders were grouped with EOS and VEOS in the childhood psychosis category which endured throughout the decade, making epidemiological states imprecise (Da Fonseca, 2009; Rutter, 1972).

Because of the rarity and severity of the disorder, VEOS and EOS require the combination of antipsychotic medication, a close follow-up of the patient, and psychological and psychosocial interventions (Dumas and Bonnot, 2013; McClellan, 2018; Remschmidt and Theisen, 2012). The diagnostic criteria are the same throughout all the person's life stages, but there are some known differences in the evidence about the use of antipsychotics by young patients, and psychosocial follow-up after the first episode is especially important for them in their future outcomes (Anagnostopoulou et al., 2019; Lee et al., 2020).

Documents that compile recommendations to the treatment of disorders like VEOS and EOS, such as clinical practice guidelines (CPG), can help decision-making and lead the practitioners to more evidence-based decisions into their practice (Keiffer, 2015; Pantoja and Soto, 2014). However, there is still a deficiency in the use of such documents by health professionals, due to the overwhelming number of documents, conflicting recommendations, the lack of knowledge on how they can be implemented, resistance to changing their practices, and a perception of the guidelines' use as a "too rigid and simplified" way of doing medicine (Graham, 2014; Keiffer, 2015; Shekelle, 2018).

To overcome these challenges and implement better practices in health services, especially in the mental health area, practitioners should have access to high-quality CPG and trustworthy recommendations. Systematic assessments of these documents can help summarize the knowledge gaps and inconsistencies and indicate the best documents that can be used and/or adapted to clinical practice by using quality appraisal instruments, such as the Appraisal of Guidelines Research and Evaluation (AGREE) tools (Johnston et al., 2018).

The AGREE II tool was launched in 2009 and is the current version of the tool developed in 2003 by a group of international guideline developers and researchers to address the high variability in the quality of the CPGs (Brouwers et al., 2010a; Brouwers et al., 2010b, c). Later, in 2019, after many researchers realize that high-quality CPGs could not guarantee

the quality and trustworthiness of their recommendations, the AGREE Consortium launched the AGREE Recommendation Excellence (AGREE-REX) to help them assess the quality of the recommendations (Brouwers et al., 2010a; Brouwers et al., 2020; Florez et al., 2020). This tool complements the AGREE II assessment and can be used in the whole document, in groups of recommendations, and/or in specific recommendations (AGREE-REX Research Team, 2019).

This kind of assessment of CPGs was lacking for schizophrenia in children and adolescents and had the potential of improving the treatment of these young patients. With this study, we wanted to summarize the existent CPGs for schizophrenia in children and adolescents, to determine their quality using the AGREE II tool, to assess the quality of the recommendations present on them using the AGREE-REX tool, and to compare the recommendations to see if the high-quality CPGs provided the best recommendations.

2 Material and methods

The protocol for this study was previously published in an open-access journal (Alves et al., 2020) (**Appendix 2**) before the beginning of the study. The methodological survey was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under protocol no. CRD42020164899.

2.1 Study design

The present study has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement **(Appendix 3**).

2.3 Eligibility criteria

2.3.1 Inclusion criteria

Following the recommendations of Johnston *et al.* (2019) in their methodological paper for systematic reviews of guidelines, we decided to display our eligibility criteria in the PICAR (Population & clinical indication(s), Intervention(s), Comparator(s), Attributes of CPG, Recommendation characteristics) format instead of the usual PICO (Population, Intervention(s), Comparator(s), Outcome(s)) format (**Table 1**).

Table 1 - Eligibility criteria on the population & clinical areas, interventions, comparators, attributes of CPG, and recommendation characteristics (PICAR) statement.

PICAR Elements	Criteria

Population & Clinical area (s)	• Children and adolescents (age <18 years) with schizophrenia
	• Treatment for:
	  ○ First episode of psychosis;
	  ○ Acute episodes of psychosis;
	  ○ Relapse episodes of psychosis;
	  ○ Chronic treatment of psychosis.

Interventions	Psychosocial; Psychological; and Pharmacological:
Comparators	• No comparator • Any antipsychotic medication • Any psychosocial intervention towards the treatment of schizophrenia in children and adolescents; • Any psychological intervention towards the treatment of schizophrenia in children and adolescents.
Attributes of CPG	• Language: Any language • Publishing region: Any region • Publication year: from 2004 (5 years before the latest version of the AGREE II instrument) to December 2020 • Version: Only the latest version of CPG is of interest • Development process: Either ADAPTE CPG or newly developed CPG • System of rating evidence: CPG use a system to rate the level of evidence behind recommendations • Scope: CPG primarily focused on the treatment and management of schizophrenia in children and adolescents • Recommendations: CPG will only be included if they report one or more eligible recommendations of interest.

Recommendation characteristics	• Interventions: Recommendations must explicitly discuss at least one intervention of interest:
	  ○ Psychosocial: Psychosocial interventions for mental health disorders are interpersonal or informational activities, techniques, or strategies that target biological, behavioral, cognitive, emotional, interpersonal, social, or environmental factors, to improve functioning and well-being of health.
	  ○ Psychological: Any action intended to interfere with and interrupt or modify a process, as in treatment undertaken to interrupt, manage, or alter the course of the pathological process of a disease or disorder. Action conducted by a psychotherapist to deal with a client's problems. Intervention selection is guided by the nature of the problem, the therapist's orientation, the environment, and the client's willingness and ability to proceed with the treatment. Also called psychological intervention.
	  ○ Pharmacological: Any action involving choice, prescription, use, and/or monitoring of medication for the treatment of schizophrenia in children and adolescents.
	• Comparator(s): Recommendations were not required to compare an intervention of interest to another. If such a comparison was made, the comparator must also have met specific eligibility criteria (see Comparators).

2.3.2 Exclusion criteria

Guidelines for schizophrenia caused by misuse of substances and guidelines for schizophrenia associated with other mental disorders were excluded. If there was another more up-to-date version of the guideline; the available version was incomplete or contained only a summary of the information; the document was the translation of a guideline published in another language; and if there was a consensus document, evidence summary, or algorithm, it was excluded, since they were not equivalent to guidelines.

2.4 Selection of studies

2.4.1 Data sources

The following electronic databases from 2004 to December 2020 were searched: EMBASE (Excerpta Medical Database, via Ovid); MEDLINE (via Ovid); PsycINFO (via Ovid); PubMed, Epistemonikos; Biblioteca Virtual em Saúde; Global Index Medicus. Specific databases for clinical guidelines were also searched: ECRI Institute (www.guidelines.ecri.org), National Institute for Health and Care Excellence (www.nice.org.uk), Canadian Agency for Drugs and Technologies in Health (www.cadth.ca), Canadian Medical Association (www.cma.ca), Canadian CPG Infobase: CPG Database (www.cma.ca/En/ Pages/clinical-practice-guidelines.aspx), Scottish Intercollegiate Guidelines Network (www.sign.ac.uk), Australian CPG (http://www.clinicalguidelines.gov.au/) and the Guidelines International Network (http://www.g-i-n.net/) database. The databases list was defined with the help of two experienced librarians.

2.4.2 Other data sources features

We checked the reference list of eligible studies, review studies, and secondary studies to identify other possible guidelines. Authors were contacted in case of guidelines published only in summary or where important information was missing.

2.4.3 Search strategies

The keywords were used according to the terms of the Medical Subject Headings to identify relevant studies. The search terms that were used for the databases were provided as in **Appendix 4**. The search strategy was adapted for each database consulted.

2.4.4 Determination of eligibility

References were managed in EndNote (version X8.2 New York City: Thomson Reuters, 2018), and duplicates were removed. Titles and abstracts were assessed by groups of three reviewers, independently, using a consensus approach, to check if they met the eligibility criteria. A full read of the CPG was conducted by the same reviewers, also independently, to confirm the eligibility of the guidelines. Discrepancies were resolved by consensus and a fourth reviewer assisted in the final decision if necessary. The most up-to-date guideline was used if there was a case of duplicate publications. All documents related to the guidelines (cited as supplemental documents, summaries of recommendations, and others) were searched manually by one or two reviewers.

2.5 Data extraction

The information was organized in a Microsoft Excel worksheet; the same groups of three reviewers, independently, extract the data. Discrepancies were resolved through discussion and consensus. If this process was not effective, a fourth reviewer was responsible for the tiebreaker. Previously, reviewers were calibrated by extracting at least three guidelines of different quality levels and reaching consensus. Results were discussed with a previously trained fourth reviewer. This procedure was repeated until the reviewers could extract the data.

The following data were extracted: the number of authors, year of publication, update time, organizations (government, medical society, university or other), type of guideline (formulated, adapted, updated or revised), country of development, type (diagnosis, prevention, pharmacological and non-pharmacological treatment, and/or other), treatments described, target population, design of studies included (systematic review, consensus, overview of systematic reviews and/or other), methods of recommendation formulation (consensus, not mentioned, others) and methods of classifying the quality of evidence (Grades of

Recommendation, Assessment, Development, and Evaluation (GRADE), Oxford, not mentioned or other).

2.6 Quality assessment of clinical practice guidelines

The AGREE II was used to evaluate the quality of the guidelines. The tool has been translated and validated for the Portuguese language (Brazil), and this version was used in this study. It includes six domains: (1) scope and purpose; (2) stakeholder involvement; (3) rigor of development; (4) clarity of presentation; (5) applicability; and (6) editorial independence, containing 23 items in total. Scores are on a Likert scale of 1 (totally disagree) to 7 (totally agree) for each item (Brouwers et al., 2010a; Khan and Stein, 2014).

A group of three reviewers conducted the quality assessment of the guidelines and differences between two or more scores for each item were considered as discrepant. The reviewers were previously trained by assessing a guideline provided by the "My AGREE PLUS" platform and one of the selected papers. This first assessment was discussed and after that, we conducted the rest of the assessments.

The final score was decided by consensus. In case of no consensus, a fourth reviewer helped in the final decision. The quality of the CPG was calculated for each domain as instructed by the AGREE II user manual (AGREE Next Steps Consortium, 2017). Since the six domains are independent, the scores were calculated as the sum of the individual items in each domain. The total obtained were presented as a relation percentage to the maximum possible score for each domain. The evaluation was conducted using the "My AGREE PLUS" platform (Brouwers et al., 2010a).

We considered high-quality CPG those that got ≥60% on domains associated with the reliability (domains 3 and 6) since those apply to the methodology and editorial independence, fundamental items for our evaluation.

2.7 Description, comparison, and quality assessment of the recommendations

The synthesis and comparison of recommendations were also made without addressing the level of evidence since there was variability in the evidence appraisal systems, which made the classification harder.

The assessment described and compared the psychological, psychosocial, and pharmacological recommendations of intervention. We anticipated the important influence of

culture/country on the recommendation of psychosocial and psychological interventions. If appropriate we analyzed such differences.

In this study, we compared the recommendations found in the CPG. Recommendations on treatment and classification of the level of evidence of the included CPG were extracted independently by two researchers. Disagreements between researchers were resolved by consensus; in the absence of consensus, a third investigator helped in the decision.

The recommendations were grouped into the categories: pharmacological, psychosocial, and psychological, according to their similarities through an interactive process between researchers. CPG that shared similar recommendations was noted. We evaluated if recommendations from different CPG addressed the same topics and compared them to identify differences. When two or more CPG showed conflicting recommendations, this was defined as a disagreement. We opted to describe the interventions present in all the CPG selected, to verify if the high-quality CPG presented similarities in their recommendations with the ones of lower quality.

We assessed the quality of the recommendations using the AGREE-REX instrument (AGREE-REX Research Team, 2019). This tool is divided into 3 domains: (1) clinical applicability; (2) values and preferences; and (3) implementability. It has 9 items in total and scoring is made on a 7-point Likert scale. It can be applied either in each recommendation if the user believes that there is variability in the quality of recommendations or wants to investigate selected recommendations, or in the whole guideline, if the user perceives that there is a consistency in the recommendations, is interested in all recommendations or wants to save time for any reason. It also has an optional item for suitability for use, scored on a 7-point Likert scale as well. We opted to assess groups of recommendations (psychological, psychosocial, and pharmacological) in pairs, using a consensus-based approach, allowed by the instrument.

The assessment of recommendations was conducted in pairs, independently, using a consensus whenever there was a discrepancy. If the discrepancy could not be solved, we reached a third reviewer to help in the final decision in a process similar to the one conducted to the guidelines assessment. The assessors were previously trained; they assessed one of the selected documents and discussed the results and possible doubts before conducting the rest of the assessments. The scoring was conducted in a similar way to the AGREE II scoring, following the AGREE-REX manual (AGREE-REX Research Team, 2019).

2.8 Data synthesis

Descriptive tables were made to show the results. Statistical analyses were performed using Microsoft Excel and STATA software (V.14.2). For all AGREE II domains, descriptive statistics were calculated as mean (SD) only.

2.9 Changes after protocol publication

Since we have adopted a consensus approach for the discrepant scores of AGREE II, which was also used with the AGREE-REX scoring, the ICC analysis of agreement between reviewers, previewed in the protocol (Alves et al., 2020), was not conducted. Also, because of the low number of selected CPG for the final evaluation and extraction, the assessment of changes and improvements in the quality of guidelines over time, after the latest version of the AGREE instrument, using the Wilcoxon Rank-Sum test (Mann-Whitney test), was not conducted.

3 Results

From 3,182 titles retrieved in the database search, 2,030 records were screened and 29 were selected for full-text reading. After this phase, 4 were included (**Figure 1**).

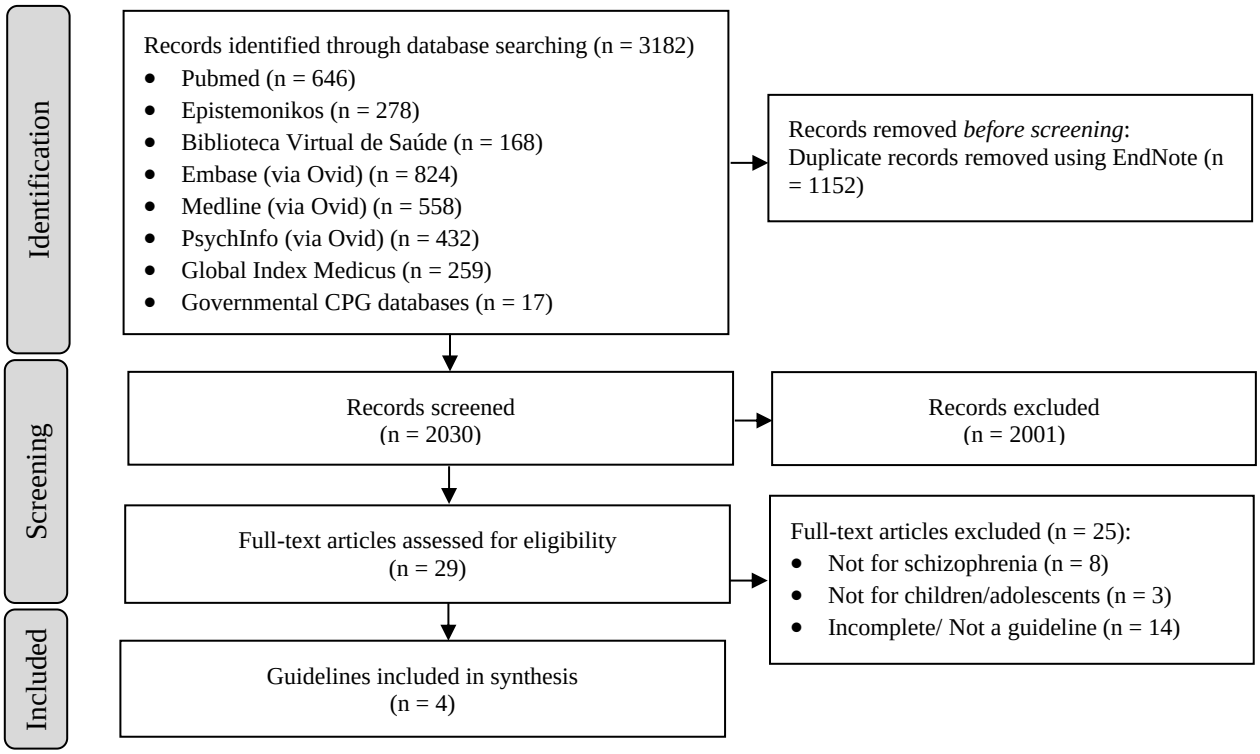

Figure 1 – Flowchart of guideline identification.

Of the selected CPG, two were newly elaborated, one was elaborated using the ADAPTE methodology, and one did not mention the methodology for elaboration. The evidence appraisal system was different in all of them; only the National Institute for Health and Care Excellence (NICE) CPG (2016) presented a similar appraisal system with the Canadian CPG (Abidi et al., 2017; Addington et al., 2017; Crockford and Addington, 2017; Lecomte et al., 2017; Norman et al., 2017; Pringsheim and Addington, 2017) because it was used in the ADAPTE process of this last one (**Table 2**).

Table 2 – Characteristics of the selected documents

Title, Year	National Society and/or authors (Country)	Scope and key questions	Methodological approach	Evidence appraisal system
Australian Clinical Guidelines for Early Psychosis, 2016	Orygen/The National Centre of Excellence in Youth Mental Health (Australia)	This guideline was developed to address clinical 'best practice' in early psychosis prevention and intervention and to serve as a reference for individuals outside specialist mental health services, particularly in the primary health care sector, and provide an optimized service provision, while also providing a real-world focus.	Evidence- and consensus-based	NHMRC grades of recommendation
Psychosis and schizophrenia in children and young people, 2016	NICE/ National Collaborating Centre for Mental Health (United Kingdom)	This guideline covers recognizing and managing psychosis and schizophrenia in children and young people. It aims to improve early recognition of psychosis and schizophrenia so that children and young people can be offered the treatment and care they need to live with the condition.	Evidence- and consensus-based	NICE Strength of recommendations (GRADE adaptation)
Canadian Schizophrenia Guidelines, 2017	Pringsheim *et al.* (Canada)	To provide evidence-based recommendations for the treatment of schizophrenia and schizophrenia spectrum disorders that are adapted to the Canadian Health Care System. The guideline addresses the treatment of schizophrenia from its onset in youth and includes a section on the emerging field of intervention in those at clinical high risk of developing schizophrenia.	ADAPTE	NICE Strength of recommendations (GRADE adaptation)/ GRADE
Clinical Practice Guidelines for the Management of Schizophrenia in Children and Adolescents, 2019	Grover *et al.* (India)	To provide a broad framework for the assessment and management of patients with EOS, and these may have to be tailored to the needs of the individual patient.	N/A*	N/A*

*N/A = Not Available.

In the AGREE II appraisal, the Canadian and the NICE CPG had higher scores, but only the NICE CPG scored more than 60% in domains 3 and 6. The Orygen CPG (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016) had higher scores only in domains 1 and 4 and the Grover & Avasthi (2019) CPG had all scores under 60% (**Table 3**).

Table 3 – AGREE II scores of the selected clinical practice guidelines for schizophrenia in children and adolescents

Author (Year)	Domain 1 (%)	Domain 2 (%)	Domain 3 (%)	Domain 4 (%)	Domain 5 (%)	Domain 6 (%)	Overall assessment (%)
Orygen (2016)	81.5	51.9	48.6	75.9	47.2	30.6	55.6
NICE (2016)	100.0	100.0	95.1	100.0	68.1	97.2	100.0
Pringsheim *et al.* (2017)	93.1	84.7	81.8	87.5	19.8	85.4	70.8
Grover & Avasthi (2019)	44.4	7.4	7.6	64.8	1.4	58.3	16.7
Mean ± SD	**79.7 ± 24.8**	**61.0 ± 41.0**	**58.3 ± 39.0**	**82.0 ± 15.1**	**34.1 ± 29.4**	**67.9 ± 29.7**	**60.8 ± 34.7**

SD = Standard Deviation

In **Tables 4-6**, the recommendations contained in each guideline were described, divided into pharmacological, psychosocial, and psychological categories, and in the first episode of psychosis, acute phase, relapses, and chronic treatment recommendations. Pharmacological recommendations were described for all treatment phases in all CPG, but the psychological and psychosocial ones were mostly focused on the chronic treatment with only the NICE and the Orygen CPG addressing all the phases.

Table 4 – Pharmacological recommendations described in the selected guidelines

Treatment addressed	Clinical Practice Guidelines			
	Orygen, 2016	**NICE, 2016**	**Grover & Avasthi, 2019**	**Pringsheim *et al.*, 2017**
First episode of psychosis	●	●	●	●
Specified	●	●	●	●
Physical measurements and examination before medication start	●	●	●	●
First-generation antipsychotic medication	●			
Non-specified	●	●	●	●
Oral antipsychotic medication	●	●	●	●
Long-acting injectable antipsychotic medications	●			
Communication on possible side effects	●	●		●
Communication on therapeutic benefits	●	●		●
Monitoring and recording of the treatment		●		●
Regular review of medication	●	●		●
Not available				
Acute Phase	●	●	●	●
Specified	●	●		
Aripiprazole for people between 15 to 17 intolerant/non-responsive to risperidone		●		
Benzodiazepines for sedation	●			
Amisulpride for first episode non-affective psychosis	●			
Quetiapine for first episode non-affective psychosis	●			
Risperidone for first episode non-affective psychosis	●			
Ziprasidone for first episode non-affective psychosis	●			
Olanzapine (caution use) for non-responsive patients for first episode non-affective psychosis	●			
Clozapine for non-responsive patients for first episode non-affective psychosis	●			
Lithium carbonate for mood-stabilization in first episode affective psychosis	●			
Risperidone + Benzodiazepine for first episode affective psychosis	●			
Quetiapine + Benzodiazepine for first episode affective psychosis	●			
Ziprasidone + Benzodiazepine for first episode affective psychosis	●			
Aripiprazole + Benzodiazepine	●			
Olanzapine (caution use) for non-responsive patients to other SGA for first episode affective psychosis	●			
Sodium valproate to non-responsive patients to lithium	●			

	carbonate for first episode affective psychosis				
	Antidepressant plus low-dose SGA for psychotic depression	●			
	Acute Phase	●	●	●	●
	Specified	●	●		
	Mood stabilizer (preferably lithium carbonate or lamotrigine) or quetiapine for psychotic depression	●			
	Non-specified		●	●	●
	Oral antipsychotic medication		●	●	
	High-potency antipsychotic medication (with caution)		●		●
	Review of antipsychotic medication				●
	Monitoring of antipsychotic medication			●	
	Relapses	●	●	●	●
	Specified				
	Non-specified	●	●	●	●
	Increase or recommence of antipsychotic medication in early signs of relapse	●			
	Oral antipsychotic medication				●
	Communication on possible relapse episodes after an acute episode				●
	Communication on possible relapse episodes after medication withdrawn	●	●		●
	Monitoring after medication withdrawn		●	●	●
	Review of antipsychotic medication	●		●	●
	Chronic treatment	●	●	●	●
	Specified	●		●	●
	Second-generation antipsychotic medication			●*	
	Clozapine to non-respondent children and adolescents	●		●	●
	Clozapine for suicidality	●			
	Non-specified	●	●	●	●
	Oral antipsychotic medication				●
	Monitoring of physical health	●		●	●
	Communication antipsychotic medication side-effects	●			●
	Monitoring and management of antipsychotic medication side-effects		●		●
	Regular review of medication	●	●		
	Addition of a second antipsychotic medication to clozapine non-respondent children and adolescents		●		
	Multidisciplinary review to clozapine non-respondent children and adolescents	●	●		

*Except Clozapine.

Table 5 – Psychosocial recommendations described in the selected guidelines

Treatment addressed	Clinical Practice Guidelines			
	Orygen, 2016	**NICE, 2016**	**Grover & Avasthi, 2019**	**Pringsheim *et al.*, 2017**
First episode of psychosis	●	●	●	●
Adequation of treatment to the children's developmental phase	●	●	●	●
Adequation of treatment to the children's context	●	●	●	●
Group programs	●			
Early-intervention programs			●	
Acute phase	●	●	●	
Arts therapies		●		
Environmental interventions		●		
Support for carers		●		
Adequation of treatment to the children's developmental phase	●	●		
Impact evaluation before intervention		●		
Communication on the intervention process	●	●		
Shared decision-making adequate to the children's developmental phase	●	●		
Appropriate educational programs during hospital admissions		●		
Promotion of good physical health		●		
Befriending	●			
Group programs	●			
LifeSPAN programs for suicidal individuals	●			
Crisis resolution teams			●	
Relapses	●	●	●	
Offering of experience sharing after relapse or acute episode		●		
Communication on how to deal with future crises	●			
Arts therapies		●		
Group programs	●		●	
Chronic treatment	●	●	●	●
Case management	●	●	●	●
Adequate provision of education		●		
Routinely record of daytime activities		●		
Supported employment programs	●	●	●	●
Supported education programs	●	●	●	●
Social skills training			●	●
Structured behavioral lifestyle interventions	●			
Routinely review of the treatment process	●			
Group programs	●			
Peer support	●			
Family peer support	●			
Adequation of treatment to the children's developmental phase	●	●	●	●
Adequation of treatment to the children's context	●	●	●	●
Shared decision-making adequate to the children's developmental phase			●	
Group therapy			●	
Community mental health teams			●	

Table 6 – Psychological recommendations described in the selected guidelines

Treatment addressed	Clinical Practice Guidelines			
	Orygen, 2016	**NICE, 2016**	**Grover & Avasthi, 2019**	**Pringsheim *et al.*, 2017**
First episode of psychosis	●	●		●
Adequation of treatment to the children's developmental phase	●	●		●
Cognitive-behavioral therapy	●	●		●
Monitoring of outcomes in relevant areas		●		
Family intervention		●		●
Psychoeducation	●	●		●
Milieu therapy	●			
Supportive psychodynamic therapy	●			
Cognitive remediation therapy	●			
Acute phase	●	●		
Family intervention		●		
Cognitive-behavioral therapy	●	●		
Supportive therapy	●			
Relapses	●	●		
Family intervention	●	●		
Cognitive-behavioral therapy	●			
Regular risk review	●			
Chronic treatment	●	●	●	●
Family intervention		●	●	●
Cognitive-behavioral therapy		●	●	●
Regular review of the interventions		●		
Cognitive remediation therapy	●		●	●
Trauma assessment	●			
Psychoeducation	●		●	
Supportive therapy			●	

Figure 2 shows the distribution of the selected guidelines by country. Three out of four guidelines were from high-income countries. It also shows the distribution of recommendations by category (pharmacological, psychological, and psychological) and by treatment phase 9first episode, acute episode, relapses, and chronic treatment). All four CPG had recommendations for at least one of the treatment phases in each category.

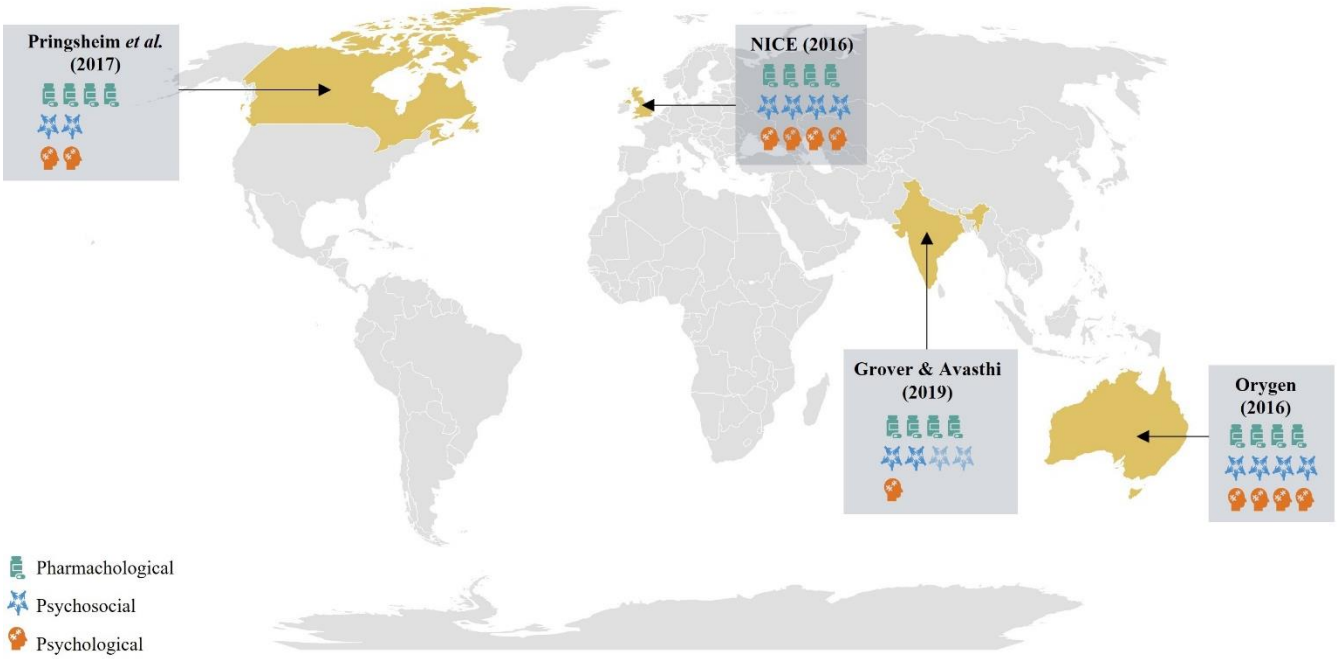

Figure 2 – Distribution of recommendations by country, category, and phase of the treatment. The icons represent each of the recommendations' categories (pharmacological, psychosocial, and psychological). Each icon represents the existence of recommendations for each of the four treatment phases assessed (first episode, acute episode, relapses, and chronic treatment). Whenever the icon is faded, it means the recommendations were incomplete for the treatment phase.

Table 7 describes the quality assessment scores obtained in the application of AGREE-REX. Psychosocial recommendations had lower scores compared to pharmacological and psychological ones, which had more similar scores. Domain 1 of clinical applicability had overall higher scores.

Table 7 – AGREE-REX quality assessment scores by treatment category

Author (Year)	Domain 1 (%)	Domain 2 (%)	Domain 3 (%)
Orygen (2016)			
Pharmachological	44.4	18.8	45.8
Psychological	44.4	29.2	45.8
Psychosocial	41.7	27.1	41.7
NICE (2016)			
Pharmachological	83.3	62.5	70.8
Psychological	86.1	60.4	70.8
Psychosocial	88.9	60.4	70.8
Pringsheim *et al.* (2017)			
Pharmachological	58.3	47.9	45.8
Psychological	61.1	43.8	41.7
Psychosocial	47.2	41.7	41.7
Grover & Avasthi (2019)			
Pharmachological	19.4	6.3	0.0
Psychological	11.1	4.2	4.2
Psychosocial	8.3	6.3	0.0
Mean ± SD	**49.5 ± 27.7**	**34.0 ± 21.9**	**39.9 ± 26.0**

SD = Standard Deviation

4 Discussion

4.1 Main Findings

Of the four CPGs assessed, two of them (NICE and Pringsheim *et al.*) had scores higher than 60% in domains 3 and 6. Two were newly developed (NICE and Orygen), one used the ADAPTE methodology (Pringsheim *et al.*), and one did not present any information about the methodology used in the development (Grover & Avasthi). About the evidence appraisal system, one of the CPGs did not inform if used any type of evidence appraisal and two presented the same system, due to one of them having used the other in the ADAPTE process.

All the CPGs presented the three types of recommendations (pharmacological, psychosocial, and psychological). Only one of them presented specific recommendations on medication, the other three had just indications about the choice of antipsychotics. About the psychosocial and psychological recommendations, two of the guidelines focused more on the first episode and chronic treatment, presenting few or no recommendations for the other

treatment phases. The highest scores in the AGREE-REX assessment were in domain 1 of clinical applicability. The psychosocial interventions had lower scores when compared to the psychological and pharmacological scores.

4.2 Comparison with previous studies

In our results, the first noticeable aspect was that most of the selected CPGs were from high-income countries. This lack of guidance from middle-low- and low-income countries was present in other critical appraisals for schizophrenia (Bradford et al., 2014; Keating et al., 2017). The ADAPTE process, used in one of the high-income countries' CPGs, could help fasten the publication of guidelines in less resourceful contexts, due to its flexible nature and possibility of being used by groups with different amounts of resources (The ADAPTE Collaboration, 2009).

There was also a variability of evidence appraisal systems used. The same problem has been found in other critical appraisals of CPGs for mental health disorders (Bradford et al., 2014; Castellani et al., 2015; Macqueen et al., 2017; Verdolini et al., 2021; Verdolini et al., 2018). This might indicate that, even though the GRADE approach is recommended in the development of this type of document (Zhang et al., 2018), it seems that it is still not well established in the CPG development processes. The use of GRADE in future developments could help mitigate this inconsistency and the standardization of evidence appraisal could benefit decision-makers, helping them compare and use the best available evidence (Castellani et al., 2015; Macqueen et al., 2017; Zhang et al., 2018).

At the AGREE II assessment, the NICE and the Canadian CPGs (Abidi et al., 2017; Addington et al., 2017; Crockford and Addington, 2017; Lecomte et al., 2017; National Institute for Health and Care Excellence, 2016; Norman et al., 2017; Pringsheim and Addington, 2017) completed the criteria to be considered of high quality. The NICE CPG for children had many recommendations adapted from the adult version (National Institute for Health and Care Excellence, 2016), which, in the assessments of CPGs for the treatment of schizophrenia in adults conducted by Bradford *et al.* (Bradford et al., 2014) and Keating *et al.* (Keating et al., 2017), was also the highest score. The Canadian CPG adapted most recommendations from the NICE CPG, which can be one of the reasons for it also having high scores.

Overall, the domain with the worst scores in the AGREE II assessment was domain 5 of applicability. This domain usually presents lower scores in critical appraisals (Bradford et

al., 2014; Florez et al., 2020; Gillespie et al., 2021; Keating et al., 2017; Macqueen et al., 2017; Verdolini et al., 2021; Verdolini et al., 2018). This is a controversial domain because information about implementation can be found in other documents outside the guideline scope and this can interfere in the scoring of the domain (Gagliardi and Brouwers, 2015). High scores in domain 5 also cannot guarantee that the CPG is implementable in a specific context (Hoffmann-Esser et al., 2017).

There was variability between the scores of the three domains of AGREE-REX in the separate assessments. Psychosocial scores were often lower than pharmacological and psychological scores in all domains. This difference between categories was also evident in the extraction of recommendations, where we noticed that psychological and psychosocial recommendations were often left aside when addressing acute episodes and relapses and had lower evidence basing them. Psychological and psychosocial interventions, although having scored very close to the ones obtained for pharmacological interventions, sometimes even surpassing them, in the domain of clinical applicability of AGREE-REX, still showed low evidence supporting these recommendations. Most of what has been produced in the past years regarding this type of intervention address the cognitive functioning of young patients with schizophrenia and lacks in showing follow-up results, as have been found in the systematic review conducted by Anagnostopoulou *et al*. (Anagnostopoulou et al., 2019).

The lack of evidence also impacts pharmacological recommendations. Many regulatory agencies around the world recommend that patients with schizophrenia younger than 13 years of age do not take any antipsychotic medication (Putignano et al., 2019). While there has been some indication of age in some recommendations through the selected CPG, most of them did not address this impossibility or even indicated that was a recommendation to off-label use. Also, we still find a barrier in the antipsychotic prescription for this age group, where most of the existing medication presented adverse drug effects, mostly weight gain, which can lead to several health problems in children and teenagers (Harvey et al., 2016; Krause et al., 2018).

4.3 Strengths and limitations

Four documents addressed our eligibility criteria and most of them were from high-income countries. The fact that the disorder studied is rare and the lack of resources and/or interest in the development of CPG in middle-low- and low-income countries is a barrier to the publication of more CPG about the topic can indicate a possible publication bias in our results.

The studies selected also lacked recent updates. The two CPG with high quality did not present an update in almost five years. Lack of updating limits the assessment since although we have a high-quality CPG, evidence is always changing, and we cannot guarantee that the CPG remains trustworthy.

In the present study, we used a structured search strategy that has been revised by two experienced librarians, and the critical appraisal was conducted in pairs or in groups of three or four assessors to avoid selection bias and minimize publication bias. We used validated and well-known instruments which assure the internal and external validity of the study.

We also used consensus scoring in our AGREE assessments, where all discrepant results were discussed between the assessors. This approach helps raise agreement between assessors and reduces potential biases.

4.4 Implications for clinical practice in health systems

The low number of CPG for the treatment of schizophrenia in childhood and adolescence combined with the uncertainty of the evidence and the low quality of such documents can contribute to no advances in the field and the heterogeneity in the treatment of this type of patient. Clinicians aiming for an evidence-based practice should have access to better documents, preferably addressing their contexts. Implementation practices should also be better described in these documents to help decision-makers in their health systems, giving clearer instructions, information about costs, equity, and context adaptation, something lacking, in different proportions, in those documents.

4.5 Implications for researchers

There is still low evidence subsiding the CPG for schizophrenia in this age range. More clinical research is needed, mainly for psychological and psychosocial treatments in acute and relapse phases, but also for treatments that are still off-label for patients with schizophrenia under 13 years of age (The Centers for Medicare & Medicaid Services (CMS) Medicaid Integrity Group (MIG), 2015). The conduction and use of network-metanalysis in the recommendations creation process also could help improve the quality and trustworthiness of the recommendations.

Countries also should subside panels of creation or adaptation of guidelines for their contexts, mostly the low and middle-low-income countries, where these types of documents are still not a reality. The use of the ADAPTE process can be a great alternative for this purpose, due to its flexible nature and possibility of being used by groups with different amounts of resources (The ADAPTE Collaboration, 2009).

5 Conclusion

CPGs for schizophrenia regarding the treatment of children and adolescents are still incipient. There are few publications about the subject, lacking both clinical studies and new CPGs, mostly for countries of middle-low or low income. The quality of the documents is overall low, and the report of recommendations has still much to improve, mostly in psychological and psychosocial areas. There is also a lack of uniformity in care conducts present in the recommendations that contribute, in some sense, to the variability of the treatment.

The quality of the evidence and the strength of the recommendations also lack transparency. These aspects could benefit from a standardization of the evidence appraisal systems in future publications, such as the use of the GRADE approach.

Acknowledgments

The authors would like to thank the contribution of Genevieve Gore, from McGill University, who helped with the selection of databases and search strategy.

References

Abidi, S., Mian, I., Garcia-Ortega, I., Lecomte, T., Raedler, T., Jackson, K., Jackson, K., Pringsheim, T., Addington, D., 2017. Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth. The Canadian Journal of Psychiatry 629, 635-647.

Addington, J., Addington, D., Abidi, S., Raedler, T., Remington, G., 2017. Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis. The Canadian Journal of Psychiatry 629, 656-661.

AGREE-REX Research Team, 2019. The Appraisal of Guidelines Research & Evaluation—Recommendation EXcellence (AGREE-REX).

AGREE Next Steps Consortium, 2017. The AGREE II Instrument

Alves, M.R., Bergamaschi, C.C., Sorrilha, F.B., Fulone, I., Barberato-Filho, S., Mayer, R.C.F., Melo, D.O., Lopes, L., 2020. Critical appraisal and comparison of recommendations of clinical practice guidelines for treatment of schizophrenia in children and adolescents: a methodological survey protocol. BMJ Open 109, e038646.

Anagnostopoulou, N., Kyriakopoulos, M., Alba, A., 2019. Psychological interventions in psychosis in children and adolescents: a systematic review. Eur Child Adolesc Psychiatry 286, 735-746.

Bradford, A.M.D.L.H., Ávila, M.J., Bohórquez Peñaranda, A.P., García Valencia, J., Arenas Borrero, Á.E., Vélez Traslaviña, Á., Jaramillo González, L.E., Gómez-Restrepo, C., 2014. Guías de práctica clínica en esquizofrenia: evaluación mediante AGREE II. Revista Colombiana de Psiquiatría 44, 3-12.

Brouwers, M.C., Kho, M.E., Browman, G.P., Burgers, J.S., Cluzeau, F., Feder, G., Fervers, B., Graham, I.D., Grimshaw, J., Hanna, S.E., Littlejohns, P., Makarski, J., Zitzelsberger, L., 2010a. AGREE II: advancing guideline development, reporting and evaluation in health care. Canadian Medical Association Journal 18218, E839-E842.

Brouwers, M.C., Kho, M.E., Browman, G.P., Burgers, J.S., Cluzeau, F., Feder, G., Fervers, B., Graham, I.D., Hanna, S.E., Makarski, J., Consortium, A.N.S., 2010b. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ 18210, 1045-1052.

Brouwers, M.C., Kho, M.E., Browman, G.P., Burgers, J.S., Cluzeau, F., Feder, G., Fervers, B., Graham, I.D., Hanna, S.E., Makarski, J., Consortium, A.N.S., 2010c. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 18210, E472-478.

Brouwers, M.C., Spithoff, K., Kerkvliet, K., Alonso-Coello, P., Burgers, J., Cluzeau, F., Férvers, B., Graham, I., Grimshaw, J., Hanna, S., Kastner, M., Kho, M., Qaseem, A., Straus, S., Florez, I.D., 2020. Development and Validation of a Tool to Assess the Quality of Clinical Practice Guideline Recommendations. JAMA Network Open 35, e205535.

Castellani, A., Girlanda, F., Barbui, C., 2015. Rigour of development of clinical practice guidelines for the pharmacological treatment of bipolar disorder: Systematic review. Journal of Affective Disorders 174, 45-50.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J., Whiteford, H.A., 2018. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr Bull 446, 1195-1203.

Crockford, D., Addington, D., 2017. Canadian Schizophrenia Guidelines: Schizophrenia and Other Psychotic Disorders with Coexisting Substance Use Disorders. The Canadian Journal of Psychiatry 629, 624-634.

Da Fonseca, D., 2009. La schizophrénie de l'enfance. L'Encéphale, S6–S9.

Da Fonseca, D., Fourneret, P., 2018. Schizophrénie à début très précoce. Encephale 446S, S8-S11.

Dumas, N., Bonnot, O., 2013. Schizophrénies à début précoce. EMC – Psychatrie/ Pédopsychiatrie 103, 1-5.

Early Psychosis Guidelines Writing Group, EPPIC National Support Program, 2016. Australian Clinical Guidelines for Early Psychosis, 2nd ed. Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne.

Florez, I.D., Brouwers, M.C., Kerkvliet, K., Spithoff, K., Alonso-Coello, P., Burgers, J., Cluzeau, F., Fervers, B., Graham, I., Grimshaw, J., Hanna, S., Kastner, M., Kho, M., Qaseem, A., Straus, S., 2020. Assessment of the quality of recommendations from 161 clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence (AGREE-REX) instrument shows there is room for improvement. Implement Sci 151, 79.

Gagliardi, A.R., Brouwers, M.C., 2015. Do guidelines offer implementation advice to target users? A systematic review of guideline applicability. BMJ Open 52, e007047-e007047.

Gillespie, B.M., Latimer, S., Walker, R.M., McInnes, E., Moore, Z., Eskes, A.M., Li, Z., Schoonhoven, L., Boorman, R.J., Chaboyer, W., 2021. The quality and clinical applicability of recommendations in pressure injury guidelines: A systematic review of clinical practice guidelines. Int J Nurs Stud 115, 103857.

Graham, B., 2014. Clinical practice guidelines: what are they and how should they be disseminated? Hand Clin 303, 361-365, vii.

Grover, S., Avasthi, A., 2019. Clinical Practice Guidelines for the Management of Schizophrenia in Children and Adolescents. Indian Journal of Psychiatry 618, 277-293.

Harvey, R.C., James, A.C., Shields, G.E., 2016. A Systematic Review and Network Meta-Analysis to Assess the Relative Efficacy of Antipsychotics for the Treatment of Positive and Negative Symptoms in Early-Onset Schizophrenia. CNS Drugs 301, 27-39.

Hoffmann-Esser, W., Siering, U., Neugebauer, E.A., Brockhaus, A.C., Lampert, U., Eikermann, M., 2017. Guideline appraisal with AGREE II: Systematic review of the current evidence on how users handle the 2 overall assessments. PLoS One 123, e0174831.

Johnston, A., Hsieh, S.-C., Carrier, M., Kelly, S.E., Bai, Z., Skidmore, B., Wells, G.A., 2018. A systematic review of clinical practice guidelines on the use of low molecular weight heparin and fondaparinux for the treatment and prevention of venous thromboembolism: Implications for research and policy decision-making. PLOS ONE 1311, e0207410.

Johnston, A., Kelly, S.E., Hsieh, S.C., Skidmore, B., Wells, G.A., 2019. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol 108, 64-76.

Keating, D., McWilliams, S., Schneider, I., Hynes, C., Cousins, G., Strawbridge, J., Clarke, M., 2017. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. BMJ Open 71, e013881.

Keiffer, M.R., 2015. Utilization of clinical practice guidelines: barriers and facilitators. Nurs Clin North Am 502, 327-345.

Khan, G.S.C., Stein, A.T., 2014. Adaptação transcultural do instrumento Appraisal of Guidelines for Research & Evaluation II (AGREE II) para avaliação de diretrizes clínicas. Cadernos de Saúde Pública 305, 1111-1114.

Krause, M., Zhu, Y., Huhn, M., Schneider-Thoma, J., Bighelli, I., Chaimani, A., Leucht, S., 2018. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol 286, 659-674.

Lecomte, T., Abidi, S., Garcia-Ortega, I., Mian, I., Jackson, K., Jackson, K., Norman, R., 2017. Canadian Treatment Guidelines on Psychosocial Treatment of Schizophrenia in Children and Youth. The Canadian Journal of Psychiatry 629, 648-655.

Lee, E.S., Kronsberg, H., Findling, R.L., 2020. Psychopharmacologic Treatment of Schizophrenia in Adolescents and Children. Child and Adolescent Psychiatric Clinics of North America 291, 183-210.

Macqueen, G., Santaguida, P., Keshavarz, H., Jaworska, N., Levine, M., Beyene, J., Raina, P., 2017. Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. The Canadian Journal of Psychiatry 621, 11-23.

McClellan, J., 2018. Psychosis in Children and Adolescents. J Am Acad Child Adolesc Psychiatry 575, 308-312.

National Institute for Health and Care Excellence, 2016. Psychosis and schizophrenia in children and young people: recognition and management. National Institute for Health and Care Excellence, Leicester.

Norman, R., Lecomte, T., Addington, D., Anderson, E., 2017. Canadian Treatment Guidelines on Psychosocial Treatment of Schizophrenia in Adults. The Canadian Journal of Psychiatry 629, 617-623.

Pantoja, T., Soto, M., 2014. Guías de práctica clínica: una introducción a su elaboración e implementación. Rev Med Chil 1421, 98-104.

Pringsheim, T., Addington, D., 2017. Canadian Schizophrenia Guidelines: Introduction and Guideline Development Process. The Canadian Journal of Psychiatry 629, 586-593.

Putignano, D., Clavenna, A., Reale, L., Bonati, M., 2019. The evidence-based choice for antipsychotics in children and adolescents should be guaranteed. European Journal of Clinical Pharmacology 756, 769-776.

Remschmidt, H., Theisen, F., 2012. Early-onset schizophrenia. Neuropsychobiology 661, 63-69.

Rutter, M., 1972. Childhood schizophrenia reconsidered. Journal of Autism and Childhood Schizophrenia 23, 315-337.

Shekelle, P.G., 2018. Clinical Practice Guidelines: What's Next? Jama 3208, 757-758.

The ADAPTE Collaboration, 2009. The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0.

The Centers for Medicare & Medicaid Services (CMS) Medicaid Integrity Group (MIG), 2015. Atypical Antipsychotic Medications: Use in Pediatric Patients.

Verdolini, N., Hidalgo-Mazzei, D., Del Matto, L., Muscas, M., Pacchiarotti, I., Murru, A., Samalin, L., Aedo, A., Tohen, M., Grunze, H., Young, A.H., Carvalho, A.F., Vieta, E., 2021. Long-term treatment of bipolar disorder type I: A systematic and critical review of clinical guidelines with derived practice algorithms. Bipolar Disord 234, 324-340.

Verdolini, N., Hidalgo-Mazzei, D., Murru, A., Pacchiarotti, I., Samalin, L., Young, A.H., Vieta, E., Carvalho, A.F., 2018. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines. Acta Psychiatr Scand 1383, 196-222.

Zhang, Y., Akl, E.A., Schunemann, H.J., 2018. Using systematic reviews in guideline development: the GRADE approach. Res Synth Methods.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5 ed. Arlington: American Psychiatric Association; 2013.

2. Marder SR, Cannon TD. Schizophrenia. N Engl J Med. 2019;381(18):1753-61.

3. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr Bull. 2018;44(6):1195-203.

4. Driver DI, Thomas S, Gogtay N, Rapoport JL. Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: An Update. Child Adolesc Psychiatr Clin N Am. 2020;29(1):71-90.

5. McClellan J. Psychosis in Children and Adolescents. J Am Acad Child Adolesc Psychiatry. 2018;57(5):308-12.

6. Coulon N, Godin O, Bulzacka E, Dubertret C, Mallet J, Fond G, et al. Early and very early-onset schizophrenia compared with adult-onset schizophrenia: French FACE-SZ database. Brain Behav. 2020;10(2):e01495.

7. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ. 2010;182(10):1045-52.

8. Hoffmann-Esser W, Siering U, Neugebauer EA, Brockhaus AC, Lampert U, Eikermann M. Guideline appraisal with AGREE II: Systematic review of the current evidence on how users handle the 2 overall assessments. PLoS One. 2017;12(3):e0174831.

9. Hoffmann-Esser W, Siering U, Neugebauer EAM, Lampert U, Eikermann M. Systematic review of current guideline appraisals performed with the Appraisal of Guidelines for Research & Evaluation II instrument-a third of AGREE II users apply a cut-off for guideline quality. J Clin Epidemiol. 2018;95:120-7.

10. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ. 2010;182(10):E472-8.

11. AGREE-REX Research Team. The Appraisal of Guidelines Research & Evaluation—Recommendation EXcellence (AGREE-REX) 2019. Available from: https://www.agreetrust.org/wp-content/uploads/2019/04/AGREE-REX-2019.pdf.

12. McClellan J, Stock S, American Academy of C, Adolescent Psychiatry Committee on Quality I. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013;52(9):976-90.

13. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol. 2018;28(6):659-74.

14. Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. J Child Adolesc Psychopharmacol. 2016;26(5):410-27.

15. Dumas N, Bonnot O. Schizophrénies à début précoce. EMC – Psychatrie/ Pédopsychiatrie. 2013;10(3):1-5.

16. National Institute for Health and Care Excellence. Psychosis and schizophrenia in children and young people: recognition and management. Leicester: National Institute for Health and Care Excellence; 2016.

17. Da Fonseca D, Fourneret P. Schizophrénie à début très précoce. Encephale. 2018;44(6S):S8-S11.

18. Chen L, Selvendra A, Stewart A, Castle D. Risk factors in early and late onset schizophrenia. Compr Psychiatry. 2018;80:155-62.

19. Jaafari M, Tabril T, Ouraghene A, Aarab C, Rammouz I, Aalouane R. Behavior disorders in the childhood and adolescence of schizophrenic patients: A retrospective study. Encephale. 2019;45(3):221-5.

20. Fourneret P, Da Fonseca D. The schizophrenic's chilhood. Encephale. 2018;44(6S):S12-S6.

21. Masi G, Liboni F. Management of Schizophrenia in Children and Adolescents: Focus on Pharmacotherapy. Drugs 2011;2(71):179-208.

22. Dickson H, Roberts RE, To M, Wild K, Loh M, Laurens KR. Adolescent trajectories of fine motor and coordination skills and risk for schizophrenia. Schizophr Res. 2020;215:263-9.

23. Skikic M, Arriola JA. First Episode Psychosis Medical Workup: Evidence-Informed Recommendations and Introduction to a Clinically Guided Approach. Child Adolesc Psychiatr Clin N Am. 2020;29(1):15-28.

24. Da Fonseca D. La schizophrénie de l'enfance. L'Encéphale. 2009:S6–S9.

25. Remschmidt H, Theisen F. Early-onset schizophrenia. Neuropsychobiology. 2012;66(1):63-9.

26. Kaushik A, Kostaki E, Kyriakopoulos M. The stigma of mental illness in children and adolescents: A systematic review. Psychiatry Research. 2016;243:469-94.

27. Hartog K, Hubbard CD, Krouwer AF, Thornicroft G, Kohrt BA, Jordans MJD. Stigma reduction interventions for children and adolescents in low- and middle-income countries: Systematic review of intervention strategies. Social Science & Medicine. 2020;246:112749.

28. Morgades-Bamba CI, Fuster-Ruizdeapodaca MJ, Molero F. Internalized stigma and its impact on schizophrenia quality of life. Psychol Health Med. 2019;24(8):992-1004.

29. Valery K-M, Prouteau A. Schizophrenia stigma in mental health professionals and associated factors: A systematic review. Psychiatry Research. 2020;290:113068.

30. Mehta N, Clement S, Marcus E, Stona AC, Bezborodovs N, Evans-Lacko S, et al. Evidence for effective interventions to reduce mental health-related stigma and discrimination in the medium and long term: Systematic review. British Journal of Psychiatry. 2015;207(5):377-84.

31. Anagnostopoulou N, Kyriakopoulos M, Alba A. Psychological interventions in psychosis in children and adolescents: a systematic review. Eur Child Adolesc Psychiatry. 2019;28(6):735-46.

32. De Hert M, Detraux J. The Urgent Need for Optimal Monitoring of Metabolic Adverse Effects in Children and Youngsters Who Take On-label or Off-label Antipsychotic Medication. JAMA Psychiatry. 2018;75(8):771.

33. Chen S, Barner JC, Cho E. Trends in off-label use of antipsychotic medications among Texas Medicaid children and adolescents from 2013 to 2016. Journal of Managed Care & Specialty Pharmacy. 2021;27(8):1035-45.

34. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, et al. Extent and Risks of Antipsychotic Off-Label Use in Children and Adolescents in Germany Between 2004 and 2011. Journal of Child and Adolescent Psychopharmacology. 2017;27(9):806-13.

35. Organization WH. Mental health atlas 2017. Geneva: World Health Organization; 2018.

36. Zhou W, Ouyang F, Nergui OE, Bangura JB, Acheampong K, Massey IY, et al. Child and Adolescent Mental Health Policy in Low- and Middle-Income Countries: Challenges and Lessons for Policy Development and Implementation. Front Psychiatry. 2020;11:150.

37. Stein AT, Lang E, Migowski A. Implementing clinical guidelines: a need to follow recommendations based on the best evidence available. Rev Bras Epidemiol. 2018;21:e180021.

38. Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington D.C.: National Academies Press; 2011.

39. Joshi GP, Benzon HT, Gan TJ, Vetter TR. Consistent Definitions of Clinical Practice Guidelines, Consensus Statements, Position Statements, and Practice Alerts. Anesth Analg. 2019;129(6):1767-70.

40. Kredo T, Bernhardsson S, Machingaidze S, Young T, Louw Q, Ochodo E, et al. Guide to clinical practice guidelines: the current state of play. Int J Qual Health Care. 2016;28(1):122-8.

41. Murad MH. Clinical Practice Guidelines. Mayo Clinic Proceedings. 2017;92(3):423-33.

42. Shekelle PG. Clinical Practice Guidelines: What's Next? Jama. 2018;320(8):757-8.

43. Keiffer MR. Utilization of clinical practice guidelines: barriers and facilitators. Nurs Clin North Am. 2015;50(2):327-45.

44. Bhide A, Acharya G. Who should write and endorse clinical practice guidelines if our patients are to benefit from them? Acta Obstetricia et Gynecologica Scandinavica. 2018;97(12):1413-4.

45. Graham B. Clinical practice guidelines: what are they and how should they be disseminated? Hand Clin. 2014;30(3):361-5, vii.

46. Pantoja T, Soto M. Guías de práctica clínica: una introducción a su elaboración e implementación. Rev Med Chil. 2014;142(1):98-104.

47. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol. 2019;108:64-76.

48. AGREE Next Steps Consortium. The AGREE II Instrument 2017. Available from: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf.

49. AGREE Next Steps Consortium. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Quality and Safety in Health Care. 2003;12(1):18-23.

50. Makarski J, Brouwers MC. The AGREE Enterprise: a decade of advancing clinical practice guidelines. Implementation Science. 2014;9(1).

51. Florez ID, Brouwers MC, Kerkvliet K, Spithoff K, Alonso-Coello P, Burgers J, et al. Assessment of the quality of recommendations from 161 clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence (AGREE-REX) instrument shows there is room for improvement. Implement Sci. 2020;15(1):79.

52. Brouwers MC, Spithoff K, Kerkvliet K, Alonso-Coello P, Burgers J, Cluzeau F, et al. Development and Validation of a Tool to Assess the Quality of Clinical Practice Guideline Recommendations. JAMA Network Open. 2020;3(5):e205535.

APPENDIX 1 – ORIENTATIONS TO THE PRESENTATION OF DISSERTATIONS/THESIS OF THE UNIVERSITY OF SOROCABA'S GRADUATE PROGRAM IN PHARMACEUTICAL SCIENCES

ORIENTAÇÕES PARA APRESENTAÇÃO DE DISSERTAÇÕES/TESES DO PROGRAMA DE PÓS-GRADUACÃO EM CIÊNCIAS FARMACÊUTICAS DA UNIVERSIDADE DE SOROCABA

As dissertações/teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s).

Os trabalhos de investigação que possam resultar em patentes poderão ser apresentadosna forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de **pelo menos um** artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s)respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

As teses entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de **pelo menos dois artigos** em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

Para aclarar membros da banca que desconhecem esta versão alternativa da dissertação/tese recomenda-se anexar este documento no final das versões encaminhadas aos membros da banca.

A dissertação/tese no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Quadro 1 - Elementos para a construção da dissertação no formato de artigo(s) científico(s).

Elementos pré-textuais	*1. Folha de rosto*
	2. Errata (Opcional)
	3. Folha de aprovação
	4. Dedicatória (Opcional)
	5. Agradecimentos (Opcional)
	6. Epígrafe (Opcional)
	7. Resumo na língua vernácula

	8. Resumo em inglês (Abstract)
	9. Lista de abreviaturas e siglas; lista de tabelas e lista de símbolos (opcionais). Estas listas não devem conter as informações apresentadas nos artigos científicos.
	10. Sumário
Elementos textuais	*11. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.
	12. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	13. Objetivos: geral e específico
	14. Material e Métodos (opcional). Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.
	15. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere- se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	16. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	17. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.

Elementos pós-textuais	*18. Referências:* Devem seguir as normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	19. Apêndices (Opcional)
	20. Anexos (Opcional)

APPENDIX 2 – PROTOCOL PUBLISHED IN THE BMJ OPEN JOURNAL (DOI: 10.1136/ BMJOPEN-2020-038646)

Open access Protocol

BMJ Open

Critical appraisal and comparison of recommendations of clinical practice guidelines for treatment of schizophrenia in children and adolescents: a methodological survey protocol

Maíra Ramos Alves,[1] Cristiane de Cássia Bergamaschi,[1] Flávia Blaseck Sorrilha,[1] Izabela Fulone,[1] Silvio Barberato-Filho,[1] Rejane Coan Ferretti Mayer,[1] Daniela Oliveira de Melo,[2] Luciane Lopes [1]

To cite: Alves MR, Bergamaschi CdC, Sorrilha FB, *et al*. Critical appraisal and comparison of recommendations of clinical practice guidelines for treatment of schizophrenia in children and adolescents: a methodological survey protocol. *BMJ Open* 2020;**10**:e038646. doi:10.1136/bmjopen-2020-038646

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-038646).

Received 20 March 2020
Revised 05 July 2020
Accepted 28 July 2020

[1]Graduate Course of Pharmaceutical Sciences, Universidade de Sorocaba, Sorocaba, São Paulo, Brazil
[2]Graduate Course of Pharmaceutical Sciences, Universidade Federal de Sao Paulo, São Paulo, São Paulo, Brazil

Correspondence to
Professor Luciane Lopes; luslopesbr@gmail.com

ABSTRACT

Introduction The number of clinical practice guidelines (CPGs) have increased substantially mainly in the paediatric area of mental health. However, little is known about the quality or how recommendations for the treatment of disorders such as schizophrenia in children and adolescents have changed over time. The aim of this study will be to assess the quality of the development of CPGs for the treatment and management of schizophrenia in children and adolescents over time using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool and to compare the recommendations and interventions described in these documents.

Methods and analysis CPGs will be identified using a prospective protocol through a systematic search of multiple databases (Medline, Embase, Health Systems Evidence, Epistemonikos, Lilacs, etc) and guideline websites from 2004 to December 2020. The quality of the guidelines will be assessed by three reviewers, independently using the AGREE II. CPGs will be considered of high-quality if they scored ≥60% in four or more domains of the AGREE II instrument. Non-parametric tests will be used to test for the change of quality over time. We will summarise the different evidence grading systems and compare the recommendations.

Ethics and dissemination Ethical approval is not required since it is a literature-based study. Future results of the research can be submitted for publication in scientific journals of high impact, peer reviewed and also published in national and international conferences. The results derived from this study will contribute to the improvement of health institutions and policies, informing about existing recommendation guidelines and about deficiencies and qualities found in those. This study may also identify key areas for future research. This study may guide the search and choice for high quality CPGs by health policy makers and health professionals and subsidise future adaptations.

Protocol registration number CRD42020164899.

Strengths and limitations of this study

- This study will add to current knowledge by highlighting clinical practice guidelines (CPGs) of great quality that we might be able to use in current clinical practice.
- We expect to identify the main characteristics and flaws of CPGs for schizophrenia in children and adolescents, which can help guide the development of recommendations guidelines of high methodological rigour for this disorder.
- The critical appraisal of the CPGs for the treatment of schizophrenia in children and adolescents was never performed.
- This study will be limited to subjective analysis of the Appraisal of Guidelines for Research and Evaluation II instrument, which can be a limiting factor.
- The wide inclusion criteria, which can provide an ample overview of the CPGs developed for the disorder, might also make synthesis of the evidence more challenging.

INTRODUCTION

Schizophrenia spectrum disorders are a group of disorders in which individuals experience perceptive distortions of reality and impairments on thinking, behaviour and affect.[1] Throughout the protocol, we have decided to focus on schizophrenia (International Classification of Diseases-10: F20), since the criteria used in the diagnosis in children and adolescents is agreed to be the same descripted in the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition) for this particular disorder.[1–3] Usually, schizophrenia diagnosis occurs in very early adulthood, being rarer in children and adolescents.[4] In this population,

onset frequently develops between 13 and 17 years of age, being prevalent in 1–2 individuals in every 1000; onsets before 13 years of age have a prevalence of 1 in every 10 000.[5]

In children diagnosed with schizophrenia, the presence of pre-morbid motor, language and social disorders is common, as well as previous learning difficulties and diagnosis of mood or anxiety disorders.[2] Among diagnosed adolescents and preadolescents, many have comorbidities such as post-traumatic stress disorder, attention deficit/hyperactivity disorder, and history of disturbing behaviours and conduct disorders.[6]

Schizophrenia in such cases is described as a psychotic disorder in which life expectancy is reduced and impairments on the social, psychological, educational and occupational spheres are frequently severe and debilitating.[7 8] The diagnosis process of schizophrenia in children and adolescents must involve a very detailed physical and psychological examination in order to exclude any possibility of organic causes for the psychosis or any kind of misdiagnosis.[2]

Because of its social impairments and stereotypical behaviours, a misdiagnosis of autism spectrum disorder is possible in children, being the presence of hallucinations and delusions what distinguish those two disorders.[3] In teenagers, the overlapping of affective symptoms (mania and depression) and psychotic symptoms (delusions, hallucinations, incoherent or non-sense speech, inappropriate behaviour) can cause difficulties in the diagnosis of schizophrenia, generally misleading to an affective disorder diagnosis.[9]

Another obstacle in the diagnosis of schizophrenia in children and adolescents is that, although psychotic symptoms are found in children with no psychopathology in a relatively high prevalence,[10] schizophrenia in this population is rare and have a lack of epidemiological data about diagnoses based on standardised clinical assessments.[2]

Psychological interventions are recommended as a first line of treatment of schizophrenia in children and adolescents, with better outcomes when applied to individuals on their first psychotic symptoms, before the onset of the disorder.[8] Although antipsychotic medication is the main form of treatment of schizophrenia, evidence of their efficacy in the treatment of this specific population is still limited.[7 8 11] Clozapine is indicated as being the most effective in comparison to other antipsychotics, even though second-generation antipsychotics have shown higher incidence of side-effects.[2 8 11]

To help in the interventions on schizophrenia young patients, guidelines have been created in the past years based on developments in the management of schizophrenia in children and adolescents.[12 13] Clinical practice guidelines (CPGs) have a significant importance in the transposition of research evidence into clinical practice, formulating health questions that are fundamental to ensure recommendations are applicable.[14] For this to be possible, the CPG must be developed according to the best available evidence.[15]

CPGs for schizophrenia in children and adolescents normally are adaptations of already existing guidelines for adult-onset schizophrenia, due to the lacking of specific evidence about this age range.[12 16 17] Implementing a CPG may take time depending on how much change is needed on the health service, becoming easier to put them into practice when they are aligned with the local priorities.[17] To assess the methodological rigour and transparency in a CPG, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was developed by an international group in 2003, and have been updated to the second version in 2009. This instrument has been widely used and offers a comprehensive, rapid and consistent assessment of CPGs.[18]

During a preliminary search, no systematic assessment that had carried out a critical appraisal on the development of CPGs for the treatment of schizophrenia in children and adolescents was found. In this study, the aim is to assess whether CPGs for the treatment and management of schizophrenia in children and adolescents have been developed with sufficient transparency and methodological quality for its implementation over time. It also aims to compare the recommendations and interventions for schizophrenia in children and adolescents described in those documents, in order to subsidise adaptations from future panellists.

METHODS AND ANALYSIS

Study design

The present systematic assessment of CPGs for schizophrenia in children and adolescents will be conducted to compare the recommendations of the interventions and the methodological quality in their development, available in these documents.

Protocol and registration

This study will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[19]

Patient and public involvement

Patients did not participate on the study design. However, by the end of the study, we aim to contact health policy makers to inform about the results and to ask to collaborate with us in the dissemination plan.

Eligibility criteria

Inclusion criteria

Overall or specific guidelines for clinical practice including psychosocial, psychological and pharmacological interventions for the treatment of children and adolescents (age <18 years) with schizophrenia will be included. Documents published from 2004 (5 years before the latest version of the AGREE II instrument) to December 2020 will be considered, with no language restrictions.

Exclusion criteria

Guidelines for schizophrenia caused by misuse of substances and guidelines for schizophrenia associated

with other mental disorders will be excluded. If there is another more up-to-date version of the guideline; the available version is incomplete or contains only a summary of the information; the document is the translation of a guideline published in another language; and if there is a consensus document, evidence summary or algorithm, it will be excluded, since they are not equivalent to guidelines.

Measured outcomes

The methodological quality of the CPGs for interventions for schizophrenia in children and adolescents will be evaluated; the scores of each domain of the AGREE II instrument,[18] associated with the methodological quality of the guidelines will be identified; and the recommendations provided by the guidelines will be described and compared.

Selection of studies

Data sources

The following electronic databases from 2004 to December 2020 will be searched: EMBASE (Excerpta Medical Database, via Ovid); MEDLINE (via Ovid); PsycINFO (via Ovid); Trip Database; Epistemonikos; Lilacs; WHO; Health Systems Evidence. Specific databases for clinical guidelines will be also searched, for example: ECRI Institute (www.guidelines.ecri.org), National Institute for Health and Care Excellence (www.nice.org.uk), Canadian Agency for Drugs and Technologies in Health (www.cadth.ca), Canadian Medical Association (www.cma.ca), Canadian CPG Infobase: CPGs Database (www.cma.ca/En/ Pages/clinical-practice-guidelines.aspx),Scottish Intercollegiate Guidelines Network (www.sign.ac.uk), Australian CPGs (http://www.clinicalguidelines.gov.au/) and Guidelines International Network (http://www.g-i-n.net/).

Other data sources features

Reviewers will check the reference list of eligible studies, review studies and secondary studies in order to identify other possible guidelines. Authors will be contacted in case of guidelines published only in summary or where important information is missing.

Search strategies

The key words will be used according to the terms of the Medical Subject Headings to identify relevant studies. The search terms that will be used for Embase (via Ovid), Medline (via Ovid and PubMed) and PsycInfo (via Ovid) are provided as online supplemental material (see online supplemental files 1 and 2). The search strategy will be adapted for each database consulted.

Determination of eligibility

References will be managed in EndNote (version X8.2 New York City: Thomson Reuters, 2018), and duplicates will be removed. Titles and abstracts will be assessed by groups of three reviewers, independently, to check if they meet the eligibility criteria. A full read of the CPG will be conducted by the same reviewers, also independently, in order to confirm the eligibility of the guidelines. Discrepancies will be solved by consensus and a fourth reviewer will be able to assist in the final decision if necessary. The most up-to-date guideline will be used if there is a case of duplicate publications. All documents related to the guidelines (cited as supplemental documents, summaries of recommendations and others) will be searched manually by one or two reviewers.

Data extraction

The information will be organised in a Microsoft Excel worksheet; the same groups of three reviewers, independently, will extract the data. Discrepancies will be resolved through discussion and consensus. If this process is not effective, a fourth reviewer will be responsible for the tiebreaker. Previously, reviewers will be calibrated by extracting at least three documents of different quality levels and reaching consensus. Results will be discussed with a previously trained fourth reviewer. This procedure will be repeated until the reviewers can extract the data.

For this study, the following data will be considered: number of authors, year of publication, update time, organisations (government, medical society, university or other), type of guideline (formulated, adapted, updated or revised), country of development, type (diagnosis, prevention, pharmacological and non-pharmacological treatment, and/or other), treatments described, target population, design of studies included (systematic review, consensus, overview of systematic reviews and/or other), methods of recommendation formulation (consensus, not mentioned, others) and methods of classifying the quality of evidence (Grades of Recommendation, Assessment, Development, and Evaluation (GRADE), Oxford, not mentioned or other).

Quality assessment of CPGs

The AGREE II will be used to evaluate the quality of the guidelines. The tool has been translated and validated for the Portuguese language (Brazil), and this version will be used in this study. It includes six domains: (1) scope and purpose; (2) stakeholder involvement; (3) rigour of development; (4) clarity of presentation; (5) applicability; and (6) editorial independence, containing 23 items in total. Scores are in Likert scale of 1 (totally disagree) to 7 (totally agree) for each item.[18 20]

A group of three reviewers will conduct the quality assessment of the guidelines and differences between two or more scores for each item will be considered as discrepant. The final score will be decided by consensus. In case of no consensus, a fourth reviewer will help in the final decision. The quality of the CPG will be calcu- lated for each domain as instructed by the AGREE II user manual. Since the six domains are independent, the scores should therefore be calculated as the sum of the individual items in each domain. The total obtained will be presented as a relation percentage to the maximum possible score for each domain. A descriptive statistical

analysis will be conducted. Agreement between reviewers will be assessed using random single-unit bidirectional intra-class correlation coefficients (ICC).[21 22] Cohen's weighted kappa will be calculated to compare with the ICC using squared weights, since we have an ordinal scale.[1–7 22] As performed by Hayawi, Graham, Tugwell and Abdelrazeq,[23] based on Cicchetti,[21] the degree of agreement between reviewers will be categorised as: ICC <0.40 poor; 0.40–0.59 moderate; 0.60–0.74 good; 0.75–1.00 excellent. CPGs will be considered of high quality if they score ≥60% in four or more domains including the domain for rigour of development. The evaluation will be conducted using the 'My AGREE PLUS' platform.[18] Previously, a training will be done to use the AGREE II instrument.

To evaluate if there was any change and improvement in the quality of guidelines over time, after the latest version of the AGREE instrument, the Wilcoxon rank-sum test (Mann-Whitney test), will be used to test for statistical significant differences in domain scores between CPGs published before and in/after 2009 (year of the AGREE II update).

Description and comparison of the recommendations of the interventions

The assessment will describe and compare the psychological, psychosocial and pharmacological recommendations of intervention. We anticipate important influence of culture/country on the recommendation of psychosocial and psychological interventions. If appropriate we will analyse such difference.

In this study, we will compare the recommendations found in high quality CPGs, this is, CPGs that get ≥60% on domains associated with the reliability (3 and 6) and applicability (5) available in the AGREE II tool. Recommendations on treatment and classification of the level of evidence of the included CPG, will be extracted independently by two researchers. Disagreements between researchers will be resolved by consensus; in the absence of consensus, a third investigator will help in the decision. Whenever available, the GRADE approach will be used for the extraction and synthesis of recommendations of the selected CPG. If GRADE is unavailable, the CPG will be classified based on the highest score in domain 3.

The recommendations will be grouped into the following topics: pharmacological, psychosocial and psychological, according to their similarities through an interactive process between researchers. CPGs that share similar recommendations will be noted. We will evaluate if recommendations from different CPGs address the same topics and will compare them to identify differences. When two or more CPGs show conflicting recommendations, this will be defined as a disagreement. Those and the level of evidence supporting them will be highlighted.

Data synthesis

Descriptive tables will be made to show the results. For all AGREE II domains, descriptive statistics will be calculated as mean (SD) and median (IQR). When needed, graphs will be plotted. The level of significance will be 5%. Statistical analyses will be performed using Microsoft Excel and STATA software (V.14.2), except inter-rater reliability (ICC and weighted kappa), that will be performed using R statistical software.

Ethics and dissemination

Since it is a literature-based study, ethical approval is not required. The results will be shared through publication in scientific journals of high impact, peer reviewed and also published in national and international conferences.

DISCUSSION

Successful implementation of recommendations should be related to the use of appropriate methodologies and rigorous strategies in the guideline development process. Thus, we will work towards the identification of high-quality CPGs that describe interventions for schizophrenia in children and adolescents or possible deficiencies observed in these documents. With this study, beyond the quality assessment of the CPGs, we hope to create a subsidy to the process of adaptation for future panellists, providing organised information to the development of high-quality CPGs.

The description of available recommendations on interventions and its supporting evidences can contribute to the choice of treatment for schizophrenia in children and adolescents. Aiming to contribute to the improvement of health institutions and policies, we expect to inform about existing recommendation guidelines, about deficiencies found in those, and make recommendations for future research.

Explicit eligibility criteria, broad and comprehensive database research, and structured evaluation for study selection comprise the method of this methodological survey. This study, however, will be limited to subjective analysis of the AGREE II instrument, which can be a limiting factor.

Contributors Study concept and design: MRA and LL. Methodology: LL. Drafting of the manuscript: MRA and LL. Review and editing of the manuscript: LL, CdCB, FBS, IF, SB-F, RCFM, DOdM.

Funding The authors have declared that no specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors was received.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Luciane Lopes http://orcid.org/0000-0002-3684-3275

REFERENCES

1 World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems, 2016. Available: https://icd.who.int/browse10/2016/en#/ [Accessed 5 Jun 2020].
2 Driver DI, Thomas S, Gogtay N, *et al*. Childhood-Onset schizophrenia and early-onset schizophrenia spectrum disorders: an update. *Child Adolesc Psychiatr Clin N Am* 2020;29:71–90.
3 American Psychiatric Association. *American psychiatric association: diagnostic and statistical manual of mental disorders*. 5th. Arlington: American Psychiatric Association, 2013.
4 Harvey PD, Isner EC, Cognition IEC. Cognition, social cognition, and functional capacity in early-onset schizophrenia. *Child Adolesc Psychiatr Clin N Am* 2020;29:171–82.
5 Armando M, Pontillo M, Vicari S. Psychosocial interventions for very early and early-onset schizophrenia: a review of treatment efficacy. *Curr Opin Psychiatry* 2015;28:312–23.
6 Chan V. Schizophrenia and psychosis: diagnosis, current research trends, and model treatment approaches with implications for transitional age youth. *Child Adolesc Psychiatr Clin N Am* 2017;26:341–66.
7 Stafford MR, Mayo-Wilson E, Loucas CE, *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* 2015;10:e0117166-e.
8 Harvey RC, James AC, Shields GE. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. *CNS Drugs* 2016;30:27–39.
9 Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, *et al*. Clinical characteristics and predictors of outcome of Schizophrenia-Spectrum psychosis in children and adolescents: a systematic review. *J Child Adolesc Psychopharmacol* 2016;26:410–27.
10 Kelleher I, Cannon M. Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol Med* 2011;41:1–6.
11 Krause M, Zhu Y, Huhn M, *et al*. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: a network meta-analysis. *Eur Neuropsychopharmacol* 2018;28:659–74.
12 Abidi S, Mian I, Garcia-Ortega I, *et al*. Canadian guidelines for the pharmacological treatment of schizophrenia spectrum and other psychotic disorders in children and youth. *Can J Psychiatry* 2017;62:635–47.
13 Grover S, Avasthi A. Clinical practice guidelines for the management of schizophrenia in children and adolescents. *Indian J Psychiatry* 2019;61:277–93.
14 Keating D, McWilliams S, Schneider I, *et al*. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. *BMJ Open* 2017;7:e013881.
15 Alonso-Coello P, Oxman AD, Moberg J, *et al*. Grade evidence to decision (ETD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ* 2016;353:i2089.
16 Abidi S. Psychosis in children and youth: focus on early-onset schizophrenia. *Pediatr Rev* 2013;34:296–306.
17 National Collaborating Centre for Mental Health (UK). *Psychosis and schizophrenia in children and young people: recognition and management*. Leicester UK: British Psychological Society, 2013.
18 Brouwers MC, Kho ME, Browman GP, *et al*. Agree II: advancing Guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839–42.
19 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
20 Khan GSC, Stein AT. Cross-cultural adaptation of the instrument Appraisal of Guidelines For Research & Evaluation II (AGREE II) for assessment of clinical guidelines. *Cad Saude Publica* 2014;30:1111–4.
21 Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol Assess* 1994;6:7–290.
22 Hallgren KA. Computing inter-rater reliability for observational data: an overview and tutorial. *Tutor Quant Methods Psychol* 2012;8:23–34.
23 Hayawi LM, Graham ID, Tugwell P, *et al*. Screening for osteoporosis: a systematic assessment of the quality and content of clinical practice guidelines, using the agree II instrument and the IOM standards for trustworthy guidelines. *PLoS One* 2018;13:e0208251.

APPENDIX 3 – PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) STATEMENT

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Cover
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	7-8
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	13-19
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	24-25
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	26
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	27
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	28-29
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	29
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	29
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	29-30

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	29
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	30
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	30
Study characteristics	17	Cite each included study and present its characteristics.	31
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	32-38
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	38-39

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	40-41
	23c	Discuss any limitations of the review processes used.	40-41
	23d	Discuss implications of the results for practice, policy, and future research.	41-42
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	24
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	24, Appendix 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	29-30
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	21
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

APPENDIX 4 – SEARCH STRATEGY

Database	Search strategy (Search conducted on 28/07/2020)	Results
Epistemonikos	(therap* OR treatment* OR tratamento* OR terap*) (schizophr* OR esquizof*) (child* OR infant* OR crianca* OR nino OR ninos OR pediatr*)	280
BVS	(therap* OR treatment* OR tratamento* OR terap*) (schizophr* OR esquizof*) (child* OR infant* OR crianca* OR nino OR ninos OR pediatr*) + filtro guias de prática clínica	168
Global Index Medicus	(tw:((therap* OR treatment* OR tratamento* OR terap*) (schizophr* OR esquizof*) (child* OR infant* OR crianca* OR nino OR ninos OR pediatr*)))	259
	(tw:((therap* OR treatment* OR tratamento* OR terap*) (schizophr* OR esquizof*) (child* OR infant* OR crianca* OR nino OR ninos OR pediatr*))) + Filtro Practice guideline	4
Pubmed	((("Child"[Mesh] OR ("Children"[all]) OR ("childhood"[all]) OR ("child"[all])) OR ("Adolescent"[Mesh] OR ("Adolescents"[all]) OR ("Adolescent"[all]) OR ("Adolescence"[all]) OR ("Teens"[all]) OR ("Teen"[all]) OR ("Teenagers"[all]) OR ("Teenager"[all]) OR ("Teenage"[all]) OR ("Teenaged"[all]) OR ("Youth"[all]) OR ("Youths"[all]))) AND ("Schizophrenia"[Mesh] OR ("Schizophrenia"[tw]) OR ("Schizophrenias"[tw]) OR ("Schizophrenic"[tw]) OR ("Schizophrenics"[tw]) OR ("Dementia Praecox"[tw])) OR ("Schizophrenia, Childhood"[Mesh])) AND (("Guideline" [Publication Type]) OR "Practice Guideline" [Publication Type] OR "Health Planning Guidelines"[Mesh] OR ("guideline*"[all]) OR "Practice Guidelines as Topic"[Mesh] OR ("Best"[all] AND "Practices"[all]) OR ("Best"[all] AND "Practice"[all]) OR recommendation*[all])	646

EMBASE, PsycINFO, MEDLINE (via Ovid) (Search conducted on 17/06/2020)				
Search	**Query**	**Items found EMBASE**	**Items found PsycINFO**	**Items found MEDLINE**
#1	Child*.mp. or exp child/ (exp child/ used in MEDLINE and Embase but not used in PsycINFO, list of other PsycINFO terms about children available if searching PsycINFO on its own but most are captured by child*.mp.)	1996534	354939	1430837
#2	MEDLINE: adolescent/ (used also in Embase but not used in PsycINFO, list of other subject headings for adolescents in PsycINFO picked up by adolescen*.mp. as a rule)	1167570	331480	1510806
	Adolescen*.mp.			
#3	Teens.mp.	7891	6251	4963
#4	Teen.mp.	6130	5518	4018
#5	Teenage*.mp.	13855	7340	8985
#6	Youth.mp.	73984	87757	51070
#7	Youths.mp.	12221	15948	9013
#8	Schizophreni*.mp. or exp schizophrenia/	164520	105359	103143
#9	Dementia Praecox.mp.	289	290	246
#10	Guideline*.mp.	439093	5887	92836
#11	MEDLINE: exp guideline/ or "practice guidelines as topic"/	519259	700	27369
	PsycINFO: Treatment Guidelines/ or Best Practices/			
	Embase: exp practice guideline/			
#12	Recommendation*.mp.	6	0	2
#13	Best adj3 Practice*.mp.	17292	11524	9319
#14	1 and 2 and 3 and 4 and 5 and 6 and 7	2732878	820384	2366394
#15	8 and 9	164606	105633	103298
#16	10 and 11 and 12 and 13	548084	21548	156195
#17	14 and 15 and 16	372	102	97