BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013881
Article Type:	Research
Date Submitted by the Author:	15-Aug-2016
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Medical management, Pharmacology and therapeutics, Evidence based practice
Keywords:	Schizophrenia & psychotic disorders < PSYCHIATRY, psychosis, antipsychotic, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Systematic review, critical appraisal and comparison of guidelines for the pharmacological treatment of first-episode schizophrenia

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Word Count (excluding title, abstract, figures and tables):

4541

ABSTRACT

Objectives

Clinical practice guidelines (CPGs) support the translation of research evidence into clinical practice. Key health questions in CPGs ensure that recommendations will be applicable to the clinical context in which the guideline is used. The objectives of this study were to identify CPGs for the pharmacological treatment of first-episode schizophrenia; assess the quality of these guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument; and compare recommendations in relation to the key health questions that are relevant to the pharmacological treatment of first-episode schizophrenia.

Methods

A multidisciplinary group identified key health questions that are relevant to the pharmacological treatment of first-episode schizophrenia. The MEDLINE and Embase databases, websites of professional organisations and international guideline repositories were searched for CPGs that met the inclusion criteria. The AGREE II instrument was applied by three raters and data extracted from the guidelines in relation to the key health questions.

Results

In total, 3299 records were screened. Ten guidelines met the inclusion and exclusion criteria. Three guidelines scored well across all domains. Recommendations varied in specificity. Side effect concerns, rather than comparative efficacy benefits, were a key consideration in antipsychotic choice. Antipsychotic medication is recommended for maintenance of remission following a first episode of schizophrenia but there is a paucity of evidence to guide duration of treatment. Clozapine is universally regarded as the medication of choice for treatment resistance. There is less evidence to guide care for those who do not respond to clozapine.

Conclusions

An individual's experience of using antipsychotic medication for the initial treatment of first-episode schizophrenia may have implications for future engagement, adherence and outcome. While guidelines of good quality exist to assist in medicines optimisation, the evidence base required to answer key health questions relevant to the pharmacological treatment of first-episode schizophrenia is limited.

KEY WORDS

Guideline, schizophrenia, psychosis, antipsychotic.

Strengths and limitations of the study

- This is the first study to assess the quality of guidelines applicable to the pharmacological treatment of first-episode schizophrenia.
- A multidisciplinary group identified key health questions that informed a clinically focussed, systematic approach to data extraction to enhance the relevance for medicines optimisation.
- Robust application of a validated tool (AGREE II) to assess the quality of clinical practice guidelines for the pharmacological treatment of first-episode schizophrenia.
- A limitation of the study is that only guidelines written in English were included.
- The application of the AGREE II instrument reflects the quality of guideline reporting which may not always indicate all information about how the guideline was developed.

INTRODUCTION

Schizophrenia is a complex mental illness that has a significant impact on the individual and their families. The lifetime risk of schizophrenia is approximately 1% and typically manifests in early adulthood.[1] The disorder is characterised by positive symptoms (such as delusions, hallucinations and disorganised speech), negative symptoms (such as social withdrawal and reduced motivation) and cognitive impairment.[2] Approximately three quarters of people who have been diagnosed with schizophrenia will experience a relapse with about one fifth going on to have long term symptoms and disability.[1 3] The life expectancy of people with schizophrenia is reduced by 15-20 years compared to those without severe mental ill-health, only 8% are in employment and the cost to society in England is estimated at £11.8 billion per year.[4]

In recent years there has been an increasing emphasis on early intervention for people experiencing psychotic symptoms and on the reduction of the duration of untreated psychosis.[5] Comprehensive programmes for the treatment of first-episode schizophrenia aim to promote recovery, improve quality of life and functional outcomes.[6] Antipsychotic medication is a key component of the treatment offered but the clinical use of these medicines differs in the management of first-episode schizophrenia in comparison to a relapse or recurrence of an established illness.[7] At first presentation, a positive experience of using medication is likely to have long term implications for adherence and outcome.[8]

Medicines optimisation is described as by the National Institute for Health and Care Excellence as a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines.[9] To promote medicines optimisation, we must ensure that

an individualised, evidence informed choice of medication is made available to service users.[9] Translating the best available evidence into practice is a challenge so Clinical Practice Guidelines (CPGs) are a useful summary of the most recent thinking in an area of clinical medicine. The Institute of Medicine describes CPGs as "*statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*".[10] Guidelines and algorithms in mental health care can improve the quality of the services offered and the safety of medication use.[11 12] Key health questions are used in guideline development processes to clarify the scope and purpose of the individual guideline.[13 14] The definition of a set of clear and focussed health questions will ensure that the recommendations are applicable to the clinical context in which the guideline is intended to be used.[14]

The quality of guidelines will have an impact on their applicability. The AGREE II tool has been used as a way of assessing the quality of guideline reporting in healthcare.[15-18] A systematic review and critical appraisal of guidelines for the treatment of schizophrenia was carried out by Gaebel *et al* in 2005.[15] At this time Gaebel *et al* did not include the pharmacological treatment of first-episode schizophrenia when comparing the guidelines. Gaebel and colleagues updated this work in 2011 by reviewing the most recent versions of CPGs that were considered to be of good quality in 2005.[16] Differences in treatment recommendations have been evaluated by various authors in relation to guidelines that apply to the United States,[19] or the difference in recommendations for single aspects of care such as maintenance treatment.[20] As guidelines are updated or new guidelines become available it is important to continue to assess their quality and understand how the growing evidence base has influenced recommendations.

The aim of this paper is to review the quality of CPGs and compare guideline recommendations to inform practice in the field of first-episode schizophrenia. We sought to do this by adopting a systematic approach to retrieving relevant guidelines; using AGREE II to assess the quality of guidelines; developing a list of key health questions relevant to the pharmacological treatment of first-episode schizophrenia and comparing guideline recommendations in relation to the key health questions identified.

METHODOLOGY

Data sources and search strategy

The PubMed and Embase databases were searched for guidelines relating to the pharmacological treatment of first-episode schizophrenia (search terms described in Supplementary Material,

Appendix 1). A number of guideline repositories and specialist websites were searched for relevant guidelines. A hand search of reference lists for all identified guidelines was conducted. The initial search was conducted for guidelines published between January 2009 and April 2016.

Inclusion and exclusion criteria

Guidelines were included if they contained recommendations about the pharmacological treatment of adults experiencing a first episode of schizophrenia. A multidisciplinary group, comprising consultant psychiatrists, pharmacists and nurses, with expertise in the care of people experiencing a first episode of schizophrenia, identified key clinical questions that a clinician would consider when taking an algorithmic approach to the use of medication for adults presenting with a first episode of schizophrenia (Table 1). These key questions then informed the selection of guidelines to be included in the analysis.

Guidelines were included if they were written in English, and made treatment recommendations based on a systematic review of the evidence in relation to adults of 18 years or older. One reviewer (DK) did an initial screen of titles and abstracts to identify potentially eligible records. Two reviewers (DK and SMcW) then completed the second screen of abstracts to identify records that would undergo full review. Where more than one record related to a single guideline development process, they were considered together.

Table 1: Key health questions in an algorithmic approach to the pharmacological treatment of the positive symptoms of schizophrenia in adults presenting to an early intervention for psychosis service.

Initial presentation

- Which antipsychotic medications should be offered for the initial management of positive symptoms associated with a first episode of schizophrenia?
- What is the recommended dose of antipsychotic medications for first-episode schizophrenia?
- What is the duration of an initial trial of an antipsychotic for people experiencing a first episode of schizophrenia?
- Which antipsychotic medication should be considered when the person has not responded to the initial antipsychotic trialled?
- How long should a second antipsychotic trial last following non-response to the initial antipsychotic medication?
- Is there a role for long acting injectable antipsychotic medications or depot antipsychotic formulations in the management of first-episode schizophrenia?
- When are combinations of antipsychotic medication an appropriate treatment strategy for people experiencing a first episode of schizophrenia?

Maintenance of remission

- Which antipsychotic medication is recommended for the maintenance of remission from positive symptoms following a first episode of schizophrenia?
- What is the dose of maintenance antipsychotic medication following a first episode of psychosis?
- What is the duration of maintenance treatment following a first episode of schizophrenia?
- Can targeted intermittent treatment with antipsychotic medication be recommended in the management of first-episode schizophrenia?

Treatment resistance

- When should clozapine be considered in the pharmacological management of first-episode schizophrenia?
- What is the recommended dose of clozapine?
- What is the recommended duration of a clozapine trial to adequately assess response?
- What strategies can be recommended for people who have had an inadequate response to clozapine treatment?

Assessment of guideline quality

The AGREE II instrument contains 23 items grouped into 6 domains; scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence.[13] The items are rated from 1 (strongly disagree) to 7 (strongly agree). Domain scores are then scaled between 0% and 100%. Following completion of the online AGREE II tutorial and practice exercise,[21] three reviewers (DK, SMcW, IS) independently applied the AGREE II criteria to each guideline. Domain scores were calculated based on the sum of all ratings within the domain and scaled by including the minimum possible score and the difference between the maximum and minimum possible scores for that domain.[21] The AGREEII score calculator from McMaster University was used to calculate the domain scores and assess inter-rater reliability by ensuring a low level of discrepancy (less than 1.5 standard deviations from the mean domain score).[22]

Comparison of guideline recommendations

Data in relation to guideline recommendations for the key health questions (table 1) were extracted by one reviewer (DK) and then a second reviewer (CH) checked the accuracy of this work.

RESULTS

Search and selection of guidelines

The search strategy identified a total of 3299 records which were screened and yielded a final number of 10 guidelines for inclusion in the analysis (Figure 1). The guidelines and their general characteristics are listed in table 2. The guideline from the World Journal for the Society of Biological Psychiatrists (WFSBP) is published in three parts but considered as one guideline.[23-25] The Royal Australia and New Zealand College of Psychiatrists (RANZCP) guideline,[26] cross references an Australian guide for the medical management of early psychosis,[27] and they are therefore considered together. The reasons for excluding guidelines included lack of documented development methodology, language other than English, that the guideline was entirely based on another guideline or that it did not address the pharmacological treatment of first-episode schizophrenia.

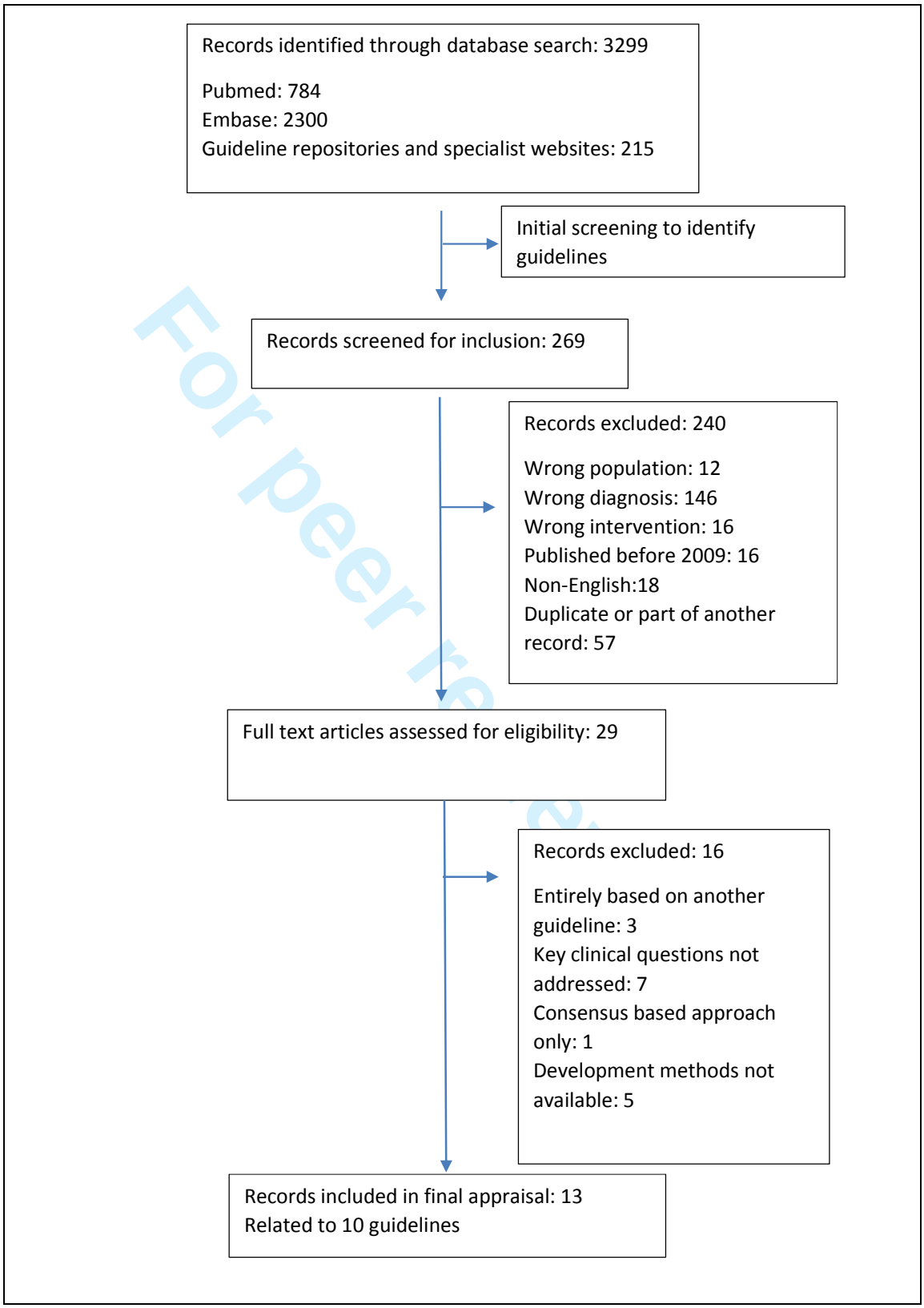

Figure 1. PRISMA diagram describing process of guideline selection.

Table 2: General characteristics of guidelines for the pharmacological treatment of first-episode schizophrenia.

Title	Author/ Institution	Country	Publication Date	End of Search Date *	Abbreviation and Reference
The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements	Schizophrenia Patient Outcomes Research Team	USA	December 2009	March 2008	PORT,[28]
Clinical Practice Guidelines for Schizophrenia and Incipient Psychotic Disorder	Ministry of Health and Consumer Affairs	Spain	March 2009	July 2007	Spain,[29]
Management of Schizophrenia in Adults	Ministry of Health, Malaysia	Malaysia	May 2009	Not described	Malaysia,[30]
Schizophrenia Clinical Practice Guidelines	Ministry of Health. Singapore	Singapore	April 2011	Not Described	Singapore,[31]
Evidence- based guidelines for the pharmacological treatment of schizophrenia: recommendations form the British Association for Clinical Psychopharmacology	British Association for Clinical Psychopharmacology	UK	2011	September 2008	BAP,[32]
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia	World Federation of Societies of Biological Psychiatry (WFSBP)	International	May 2012 to March 2015	March 2012	WFSBP,[23-25]
Management of Schizophrenia	Scottish Intercollegiate Guidelines Network	Scotland	March 2013	December 2011	SIGN,[3]
The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Schizophrenia	Harvard Medical School	USA	January 2013	Not described. Paper submitted for publication December 2011	Harvard,[33]
Psychosis and schizophrenia in adults: treatment and management	National Institute for Health and Clinical Excellence	UK	February 2014	December 2008 (for pharmacological treatment)	NICE,[34]
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the	Royal Australian and New Zealand College of Psychiatrists	Australia and New Zealand	2014 and 2016	Not described	RANZCP,[26 27]

management of schizophrenia and related disorders					
*Final search date of the systematic review of evidence that informed the guideline development process.					

Assessment of Guideline Quality

The standardised domain scores for each CPG are detailed in Table 3. The domain scores for 'Scope and purpose' were generally high with all but one guideline,[33], scoring greater than 80% (range 50-100%). There was wider variation among domain scores for stakeholder involvement ranging from 20% to 90%. The reporting of development methodology as assessed by the 'rigor of development' domain was of variable quality with a range of 41% to 91%. In the domain 'clarity of presentation' CPGs generally scored well (range 52% to 96%) in contrast to the 'applicability' domain which had wide variability (14% to 79%). The reporting of 'editorial independence' in CPGs was scored between 25% and 86%. The guidelines selected were generally of good quality with 3 guidelines recommended for use as written, 6 guidelines acceptable with modifications and one not recommended. All reviewers were in agreement with overall guideline acceptability.

Table 3: Domain scores for clinical practice guidelines (CPG) addressing the pharmacological treatment of first-episode schizophrenia using AGREE II as assessed by three raters and scaled as a percentage of the maximum possible score for each domain.

Domain	PORT (%)	Spain (%)	Malaysia (%)	Singapore (%)	BAP (%)	WFSBP (%)	SIGN (%)	Harvard (%)	NICE (%)	RANZCP (%)
Scope and Purpose	85	85	100	96	93	83	96	50	100	81
Stakeholder Involvement	54	80	93	75	63	44	90	20	89	67
Rigour of Development	69	82	74	41	56	61	91	57	84	49
Clarity of Presentation	85	89	94	94	83	52	96	78	94	83
Applicability	29	57	39	40	38	21	79	14	75	31
Editorial Independence	78	75	97	25	39	64	78	86	86	42
Overall assessment	Y	Y	Y/M	N	Y/M	Y/M	Y	Y/M	Y	Y/M
Y = Guideline is recommended for use; Y/M = Guideline is acceptable with modifications; N = Guideline is not recommended.										

Comparison of clinical practice guideline (CPG) content

Rating the quality of evidence used to support recommendations.

Guideline development groups had a range of approaches to rating the quality of the evidence and grading the strength of related recommendations. The methodologies used are listed in the supplemental material (Supplemental Material, Appendix 2). One CPG did not describe a method for grading evidence.[33] PORT took a very direct approach of needing two randomised controlled trials (RCTs) as the minimum level of evidence required to make a recommendation.[28] NICE requires the reader to understand the language used within the recommendations to interpret the strength of the recommendation.[34] Other groups used methods of varying detail and complexity to describe the strength of evidence.[3 23 26 29-32]

Recommendations in relation to key health questions at initial presentation

A table comparing the recommendation from CPGs in relation to key health questions is available in the supplementary material, Appendix 3. Guidelines broadly agree that all antipsychotics are equally effective for the treatment of positive symptoms in first-episode schizophrenia. [3 23 26 28-34] There is also a consensus that the most important consideration when helping a person make a decision about pharmacological treatment is the side effect profile of the antipsychotic. [3 23 26 28-34] Five guidelines recommend second generation antipsychotic (SGA) medications as the preferred initial choice because of the view that the side effect profiles of this group of medicines is more favourable.[23 26 29 30 33] Olanzapine is specifically excluded as a recommended initial choice of antipsychotic medication from PORT,[28] Harvard,[33] and RANZCP,[26] because of the issue of metabolic side effects and weight gain. Harvard uses the additional consideration of efficacy in the maintenance phase of treatment in excluding quetiapine because of a poorer evidence base for maintenance of remission.[33] All guideline development groups consider the evidence for the use of antipsychotic medications for first-episode schizophrenia to be of high quality even though not all antipsychotic medication have been tested in this cohort of patients. For example WFSBP notes that haloperidol is the only first generation antipsychotic (FGA) that has actually been used in trials in first-episode schizophrenia.[23] Spain,[29] and RANZCP,[26] recommend an antipsychotic free assessment period using benzodiazepines to help alleviate distress.

The most common recommendation for the duration of an initial trial of antipsychotic medication is 4 weeks.[29 31-34] Evidence that the majority of the benefit seen with antipsychotic medication will be apparent in the first two weeks of treatment is reflected in the potentially shorter trial period

suggested by some guidelines.[3 23 26] There is consensus regarding the lowest effective dose being used with a number of guidelines offering suggestions for FGA and SGA doses specific to the first episode of schizophrenia.[23 26 28 33] The only exception to this dose recommendation is that of quetiapine, which requires a dose similar to that used in acute relapse based on the interpretation of the European First Episode Study (EUFEST),[35] trial by PORT.[28]

Oral medication is recommended with parenteral formulations reserved for those who prefer this route of administration or when poor adherence is a clinical priority. [3 23 26 28-34] While monotherapy is ideal there is recognition that combinations of antipsychotic medication may be useful in certain scenarios such as clozapine augmentation. [3 23 26 28-34]

Recommendations in relation to key health questions regarding the maintenance of remission following a first episode of schizophrenia.

Recommendations regarding the duration of maintenance treatment following a first episode of schizophrenia vary between one and two years,[3 24 26 29 30 34] with some guideline development groups failing to make any recommendation.[28 31-33] RANZCP considers engagement with a first-episode schizophrenia service for up to five years to be beneficial.[26] The antipsychotic medication used for relapse prevention is generally the antipsychotic used in the acute management of symptoms at the dose that was effective in the acute phase.[3 24 28-31 33] Evidence for the superiority of medications such as olanzapine and risperidone or inferiority of quetiapine in relapse prevention is reflected in the recommendations of some guidelines.[3 24 33] Targeted, intermittent treatment is a potential strategy that reduces side effect burden and the need for adherence to longer term medication use. The evidence, however, does not support this approach because of the increased risk of relapse in comparison to continuous treatment.[24 28 32 34]

Recommendations in relation to key health questions regarding treatment resistant schizophrenia

There is consensus that the definition of treatment resistance is the failure of two trials of antipsychotic medication at optimal dose for an adequate period of time.[3 23 26 28-34] Before making a diagnosis of treatment resistance additional considerations include co-morbid substance misuse and an assessment of treatment adherence. The interpretation of recent evidence regarding the efficacy of antipsychotic medication,[36] points to the trial of olanzapine, risperidone or amisulpride as one of the two antipsychotics used before a trial of clozapine is considered.[3 33] Clozapine is universally recommended as the treatment of choice for treatment resistant schizophrenia. The variation in

doses suggested reflect the individuality of clozapine use in clinical practice, [24 28 29 31-33] with the potential for delayed response to clozapine treatment leading to the longer duration of a trial of clozapine of up to one year recommended in some guidelines.[26 28 29 32] The most common strategy suggested when there has been a partial response to clozapine despite dose optimisation is to combine clozapine with a second antipsychotic taking additional side effect profile and pharmacology into consideration.[3 24 26 29-34] Lamotrigine is also considered by some CPGs to have sufficient evidence to recommend its use as a clozapine augmentation strategy.[3 24 33] There is very little evidence to guide treatment options for those who do not have adequate symptom reduction despite clozapine augmentation.[24 30 31 33]

DISCUSSION

Assessment of Guideline Quality

This systematic review identified ten CPGs addressing the pharmacological management of first-episode schizophrenia which were assessed using the AGREE II instrument. The NICE, SIGN and Spanish guidelines scored best across all domains.[3 29 34] The CPGs assessed were generally well presented with specific statements describing the scope and purpose of each guideline. The 'rigor of development' scores for each guideline reflected the quality of methodological reporting within the text of the guideline. Supplemental information from the authors occasionally improves these scores although the Institute of Medicine has stated that such information should be publically available.[10] Plans to update the guidelines were documented for 6 of the CPGs.[3 28-31 34] Updates are currently due for two guidelines.[29 30] The majority of recommendations regarding the pharmacological treatment of first-episode schizophrenia in the NICE guidelines have not been updated since the 2009 version of the CPG.[34] Guidelines were generally weakest in the applicability domain with little offered by way of support for implementation. Examples of tools used to support applicability included versions of the CPG for service users,[3 29 34] algorithms,[26 29 33 34] and quality indicators.[30 34] Overall assessment of quality was lowest for guidelines produced by specialist organisations, where limited stakeholder involvement added to poor applicability,[23 32 33] or the reporting of development methodology was limited.[23 26 33] Within the evidence base itself, publication bias is an important consideration.[37 38] CPGs such as NICE and SIGN make significant efforts to measure the risk of bias in original trials.[3 34] Response and remission are not well defined in the guidelines even though some recommend using rating scales to assess same.

The AGREE II tool has been extensively used to evaluate the quality of CPGs in many aspects of clinical care including psychiatry.[15 17] Using the AGREE II tool helps to identify guidelines that have a transparent, systematic method of development. The AGREE II tool does not evaluate the quality of

the evidence that was used to formulate the recommendations. A comparison of CPG content would ideally involve taking the various methods by which quality of evidence is evaluated and grouping them into one standard method.[14] In most guidelines there is significant cross referencing of other similar guidelines.[3 23 29-32] SIGN and Malaysia used the NICE evidence base as their foundation.[3 30] This would appear reasonable as the NICE guideline was considered of very high quality in Gaebel *et al's* systematic review.[15] It is clear from the levels of evidence used to make recommendations in CPGs that the available research is not comprehensive enough to address all key health questions relevant to the pharmacological treatment of first-episode schizophrenia.

While the 'rigor of development' domain scores may be excellent in an AGREE assessment, the clinical utility of the subsequent recommendations vary. For example guidelines vary in the specificity of recommendations for antipsychotic use. NICE emphasise that each treatment phase be considered an individual therapeutic trial and that this will encompass any new evidence that is published in relation to pharmacological approaches.[34] In contrast, the WFSBP guideline evaluates the evidence in relation to each antipsychotic medication and Harvard makes more specific recommendations regarding the choice of antipsychotic medication.[23 33] Considering the limitations of the evidence base as it currently stands, it is reasonable to accept a transparent, consensus-based approach so that the reader can also take a view on the topic.

Development of Key Health Questions

At the beginning of a guideline development process it is important to clarify the scope and purpose of the guideline. The description of key health questions informs the development of the search strategy and helps the end user of the guideline to assess its relevance to their own clinical practice. In this study, a multidisciplinary group with expertise in the care of those with first-episode schizophrenia identified the key health questions that are relevant to the pharmacological treatment of the early stages of schizophrenia in adults. This methodology supports an evidence-informed, algorithmic approach to medicines optimisation and reflects the decisions that service-users and clinicians make in day to day clinical practice. For services that are not bound by national guidelines, this work could inform the development of local guidelines using methodology such as the ADAPTE process.[14]

Clinical Significance

Early intervention for those experiencing their first episode of schizophrenia has the potential to improve outcomes and is an important area of current research.[39-42] Early intervention services provide a range of pharmacological, psychological and educational interventions with the aims of

symptom remission and functional recovery with respect to personal, employment, educational and social outcomes.[43] Antipsychotic medication is a key component of care.[6] The clinical use of medication differs in this cohort of patients, who tend to be more sensitive to the effects of antipsychotic medication and more vulnerable to adverse effects than those in later phases of the illness.[35] Specific guidelines that address the key health questions relevant to the pharmacological treatment of first-episode schizophrenia are therefore required.

The Clinical Antipsychotic Trials of Intervention Effectiveness study (CATIE),[44] and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS),[45] began a challenge to the predominant theory that second generation antipsychotics (SGAs) were superior in efficacy and tolerability to first generation medications. Subsequent research among those experiencing their first episode of schizophrenia demonstrated the increased sensitivity to metabolic side effects of SGAs without greater efficacy while the concerns regarding the neurological side effects of first generation antipsychotics (FGAs) remain.[35 46] Navigating the varying side effect profiles of individual antipsychotic medicines has become the clinical priority when choosing the most appropriate medication in first-episode schizophrenia. Adverse effects have a significant impact on quality of life and adherence to medication,[47 48] and this must be balanced against the fact that residual symptoms also have an impact on quality of life.[49] The risk of long term neurological side effects such as tardive dyskinesia with FGAs has led to a consensus among some guideline development groups that SGAs are preferable in first-episode schizophrenia.[23 26 29 30 33] Where FGAs are chosen, low potency FGAs such as chlorpromazine are preferred. [3 23 32] Guidelines that relegate olanzapine to second line treatment do so because of the relatively high risk of metabolic side effects and weight gain in particular.[26 28 33] Recent evidence, however, suggests that there may be some efficacy benefit for individual SGAs including olanzapine both in the acute phase and for maintenance treatment of established recurrent schizophrenia.[45] This evidence has been interpreted in guidelines by suggesting that risperidone, olanzapine or amisulpride should be used as one of the two antipsychotics recommended before a trial of clozapine is considered. As new medications become available we need to evaluate their potential place in therapy for those experiencing a first episode of schizophrenia.

According to NICE "*shared decision-making is an essential part of evidence-based medicine, seeking to use the best available evidence to guide decisions about the care of the individual patient, taking into account their needs, preferences and values*".[9 50] While all guidelines recommend involving the person in the choice of antipsychotic medication thus empowering them to take an active part in their own care, there is little in the way of support for this process provided. A patient version is available for three of the guidelines to aid accessibility to the public.[3 29 34] Results from the United

Kingdom National Audit of Schizophrenia suggest that 59% of people using the mental health services for the management of schizophrenia did not feel involved in decision making about treatment.[51] The inclusion of tools such as decision aids in guidelines may improve their applicability and make a collaborative approach to care more feasible in clinical practice.[52]

Approximately 20% of those who meet the diagnostic criteria for a first episode of schizophrenia will not go on to experience any subsequent episodes.[1] The optimal duration of treatment following a first episode of schizophrenia is therefore an important health question. In one recent study the relapse rate for those who discontinued medication following 18 months of treatment (and were in clinical remission for more than 12 months with 6 months or more of functional recovery) was twice that of those who continued maintenance antipsychotic medication over the three year study period.[53] There is evidence of benefit for service users who remain in contact with an early intervention service for up to 5 years compared to those who do not.[39] Wunderink and colleagues have suggested that shorter periods of antipsychotic use should be used, arguing that despite reoccurrence of symptoms, quality of life at seven year follow up was better for those who had discontinued medication at six months than those who received maintenance antipsychotic medication.[54] These findings have not been replicated and current practice supports maintenance treatment with informed choices to be made at an individual level regarding continuation of antipsychotic medication at approximately two years following symptom remission of the first episode.[55]

Clozapine is universally accepted by guideline development groups as the antipsychotic of choice for treatment resistant schizophrenia. Approximately to 60% of those who are considered treatment resistant will respond to clozapine.[56] Leucht *et al's* analysis of the efficacy of antipsychotic medication in the acute phase of multi-episode schizophrenia showed the relative benefit of clozapine.[36] The use of clozapine is supported by open label studies, cohort studies and database studies with important positive outcomes such as reduced hospitalisation.[44 45 57] However, in a recent multivariate meta-analysis of randomised controlled trials comparing clozapine and other antipsychotic medication, the Cochrane Collaboration failed to find any significant efficacy difference in treatment resistant schizophrenia.[58] The authors also highlighted the many limitations of RCTs in the area of treatment resistance including varying definitions of treatment resistance, dose of antipsychotics and the difficulty of blinding to clozapine treatment.

CPGs are not intended to dictate all aspects of care for patients. Individual factors such as personal preferences, co-morbidity, concurrent medications, and previous experience with medication will have an impact on the choices made. Although guidelines and algorithms in mental health care can

improve the quality of medication use,[11 12] CPGs are not always used in practice.[59-61] In the Recovery After an Initial Schizophrenia Episode (RAISE) study, the authors identified 39% of the sample who could have benefitted from a medication review because prescribing practices were not in line with current guidelines in the United States.[62] For example, the use of olanzapine was relatively high even though it is specifically not recommended in a first episode of schizophrenia by the PORT guidelines. Despite the importance placed on early use of clozapine in CPGs, evidence suggests it is under-prescribed with many different strategies being used before clozapine is offered.[63 64] Clozapine's effectiveness may diminish if used later in the illness making it vitally important to identify treatment resistance and manage it appropriately as early as possible.[65] Within the setting of an early intervention service it may be feasible to implement guidelines more effectively when they are relevant to those experiencing a first episode of schizophrenia, are facilitated by local buy-in, and reflect a multidisciplinary approach.[59]

Strengths and Limitations

This is the first study to assess the quality of guidelines applicable to the pharmacological treatment of first-episode schizophrenia. The clinical use of antipsychotic medication as part of the early intervention model of service delivery is an important topic of current research. A strength of this study is the identification of key health questions that are relevant to clinical practice and the comparison of guideline recommendations in relation to these key health questions. The subjectivity inherent in the application of the AGREE II tool is reduced by the independent scoring of CPGs by three raters and by further measuring any marked discrepancy between scores. While every effort was made to include all relevant guidelines for the treatment of first-episode schizophrenia, it is possible that some have been inadvertently excluded. We only included guidelines written in the English language. Many of the guidelines included were published more than five years ago and would therefore be considered out of date according to the standards of the National Guidelines Clearing House. The AGREE tool includes an assessment of bias in relation to statements of conflict of interest for those involved in guideline development and stakeholder involvement. Even if conflicts of interest were declared, it was difficult to ascertain how this was managed and how it influenced final recommendations.[66] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group have developed an Evidence to Decision (EtD) framework for CPGs that has the potential to ensure a structured, transparent approach to developing CPG recommendations.[67]

CONCLUSIONS

The aims of early intervention for those experiencing a first episode of schizophrenia are to reduce symptoms and improve outcomes. Optimal use of antipsychotic medication is critical and clinical practice differs for the first-episode cohort in comparison to those experiencing multi-episode schizophrenia. CPGs can guide medicines optimisation but it is important for the target uses to assess the quality of CPGs so that they can have confidence in the recommendations made. The AGREE II instrument is a useful way of structuring this assessment. CPGs of good methodological quality for the pharmacological treatment of first-episode schizophrenia exist but deficiencies in the evidence base make it difficult to address the key health questions relevant to medicines optimisation in clinical practice. Further research is required to guide choice and dose of medication, duration of treatment, and the management of treatment resistance.

CONTRIBUTIONS

DK developed the concept. DK, GC and SMcW contributed to the search for data. DK, SMcW and IS were involved in the application of the AGREE II tool. DK and CH participated in the extraction of data. JS and MC participated in substantive review of the manuscript.

COMPETING INTERESTS

The authors report no competing interests

FUNDING

This research received no specific financial support.

DATA SHARING STATEMENT

No additional data available

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Appendix 1. Search terms and search strategy

The search terms used for PubMed were "Psychotropic Drugs"[Mesh], "antipsychotic"[All Fields], "antipsychotics"[All Fields] "guideline"[Publication Type] "guidelines as topic"[MeSH Terms], "guidelines"[All Fields]), "guideline"[All Fields], "consensus development conference"[Publication Type] "consensus development conferences as topic"[MeSH Terms]"consensus"[All Fields] "recommend"[All Fields] "recommends"[All Fields] "recommendation"[All Fields], "recommendations"[All Fields], "Schizophrenia and Disorders with Psychotic Features"[Mesh], "schizophrenia"[All Fields], "schizophrenic"[All Fields], "schizophreniform"[All Fields] "psychosis"[All Fields], "psychotic"[All Fields], "schizoaffective"[All Fields]

The search terms used for Embase were "schizophrenia"[All Fields], "schizophrenic"[All Fields], "schizophreniform"[All Fields] "psychosis"[All Fields], "psychotic"[All Fields], "schizoaffective"[All Fields], 'schizophrenia'/exp, 'psychotropic agent'/exp, "antipsychotic"[All Fields], "antipsychotics"[All Fields], 'practice guideline'/exp, "guideline"[All Fields], "guidelines"[All Fields] "consensus"[All Fields] "recommend"[All Fields] "recommends"[All Fields] "recommendation"[All Fields], "recommendations"[All Fields],

The guideline repositories searched were the Guidelines International Network, National Guidelines Clearing House, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, Canadian Medical Association Infobase, British Columbia Ministry of Health, Australian National Health and Medical Research Council, Australian Government clinical Practice Guidelines Portal, New Zealand Guidelines Group, German National Disease Management Guideline Programme.

The specialist association websites searched were; Canadian Psychiatric Association, Canadian agency for Drugs and Technology in Health, Substance Abuse and Mental Health Services, Administration, American Psychiatric Association, Veterans Affairs United States, World Society of Biological Psychiatry, Australia and New Zealand Psychiatric Association, European Psychiatric Association, International Psychopharmacology Algorithm Project, British Association for Psychopharmacology, Texas Medication Algorithm Project, world Psychiatric Association, International Early Psychosis Association, Early Psychosis Prevention and Intervention Centre, Lambeth Early Onset Services, Early Detection and Treatment of Psychosis (TIPS) Norway, Prevention and Early Intervention for Psychosis Programme Canada, South London and Maudsley NHS Trust Prescribing Guidelines.

Appendix 2: Levels of evidence and grades of recommendation used to describe the strength of recommendations in clinical practice guidelines (CPG) addressing the pharmacological treatment of first episode schizophrenia.

PORT 2009	Spain 2009	Malaysia, 2009	Singapore 2011	BAP 2011	WFSBP, 2012	SIGN, 2013	Harvard 2013	NICE 2014	RANZCP, 2016
Must have at least 2 RCTs to make a recommendation	Ia Meta-analysis of RCTs Ib At least one RCT IIa At least one well designed non-randomised controlled prospective study IIb At least one well designed quasi-experimental study III Well designed observational studies eg comparative study, correlation study or case-control studies IV Expert opinion and clinical experience Grade A: Evidence level 1a or 1b. At least one good quality RCT. Grade B: Evidence level IIa, IIb, or III. Methodologically correct clinical trials that are not RCTs Grade C: Evidence level IV. Expert opinion in the absence of other clinical evidence.	Level 1, good strength, Meta-analysis of RCT, systematic review. Level 2, good strength. Large sample RCT Level 3, Good to fair strength. Small sample RCT. Level 4, Good to fair strength. Non-randomised controlled prospective trial. Level 5, fair strength. Non-randomised controlled prospective trial with historical control. Level 6. Fair strength. Cohort study. Level 7, Poor strength, case-controlled study. Level 8, Poor strength, Non-controlled clinical series, descriptive studies multi-centre Level 9, poor strength, Expert committees, consensus, case reports, anecdotes. **Grades of**	1++ High quality meta- analysis, systematic reviews of RCTs or RCT with very low risk of bias. 1+ Well-conducted meta-analysis, systematic reviews of RCTs or RCTS with a low risk of bias 1- Meta-analysis, systematic reviews of RCTs or RCTs with a high risk of bias 2++ High quality systematic reviews of case control or cohort studies, High quality case control or cohort studies with a very low risk of bias or confounding and a high probability that the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of bias or confounding and a moderate probability that the relationship is causal. 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.	***Causal relationships and treatment*** Category I; Meta-analysis of RCTs, at least one large good quality RCT or replicated, smaller RCTs. Category II: Small non-replicated RCT; at least one controlled study or at least one other quasi experimental study. RCT must have a control treatment arm. Category III: non-experimental descriptive studies eg comparative, correlation or case control. Category (IV) Expert committee report/ opinion/ clinical experience ***Non-causal relationships*** Category I: Evidence from large representative population samples. Category II: Evidence from small, well-designed, but not necessarily representative samples. Category III:	Category of Evidence: A: Full evidence from controlled studies: Two or more double blind RCT vs placebo and one or more RCT vs active comparator with placebo arm or well conducted non-inferiority trial. If there is an existing negative study it must be outweighed by at least 2 positive studies or a meta-analysis. B: Limited positive evidence from controlled studies. One or more RCT showing superiority to placebo or RCT vs comparator without placebo control and no negative studies exist. C Evidence from Uncontrolled studies/ case reports/ expert opinion. C1: Uncontrolled studies: 1 or more positive naturalistic study, comparison with an existing drug with sufficient sample size and no negative studies. C2: Case reports. One or more positive case reports. No negative	1++ High quality meta- analysis, systematic reviews of RCTs or RCT with very low risk of bias. 1+ Well-conducted meta-analysis, systematic reviews of RCTs or RCTS with a low risk of bias 1- Meta-analysis, systematic reviews of RCTs or RCTs with a high risk of bias 2++ High quality systematic reviews of case control or cohort studies, High quality case control or cohort studies with a very low risk of bias or confounding and a high probability that the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of bias or confounding and a moderate probability that the relationship is causal. 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.	None described	Strength of recommendation described in the language of the recommendation. <u>Must or must not</u>: Legal duty to apply recommendation of if consequences of not following recommendation are serious or life threatening. <u>Should or should not:</u> Indicates a strong recommendation. 'Offer', 'refer', 'advise' when confident that for the vast majority of patients an intervention will do more good than harm and be cost effective. Conversely 'do not offer' when confident that intervention will not be of benefit for most patients. <u>Could be used.</u> 'Consider' if confident that an intervention will do more good than harm for most patients, be cost effective but other options may be similarly cost effective. Choice of the intervention more likely to	Recommendations are either Evidence based (EBR) or consensus based (CBR). The level of evidence on which EBR is according to the National Health and Medical Research Council's levels of evidence for healthcare interventions. Level I: A systematic review of level II studies. Level II: A randomised controlled trial. Level III-1: A pseudo-randomised controlled trial. Level III-2: A comparative study with concurrent controls: non-randomised, experimental trial. Cohort studies. Case-control study. Interrupted time-series with a control group. Level III-3: A comparative study without concurrent controls. Historical control study. Two or more single-arm studies. Interrupted time series without

		Recommendation. A. At least one meta-analysis, systematic review, RCT, or evidence rated as good and directly applicable to the target population. B. Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review, or RCT. C. Evidence from expert committee reports, or opinions and/or clinical experiences of related authorities; indicates absence of directly applicable clinical studies of good quality.	3 Non-analytic studies eg case reports, case series 4 Expert opinion **Grades of Recommendation.** **A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+ applicable to target population and demonstrating overall consistency of results. **B** A body of evidence consisting principally of studies rated as 2++ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ **C** A body of evidence consisting principally of studies rated as 2+ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+	Evidence from non-representative surveys, case reports. Category IV: Evidence from expert committee reports or opinions and /or clinical opinions of respected authorities. ***Strength of recommendation*** A: Category I B Category II or extrapolated from category I C: Category III or extrapolated from category I or II D: Category IV or extrapolated from category I, II or III S: Standard of good practice	controlled studies. C3: Expert opinion or clinical experience. D: Inconsistent results. Equal number of positive and negative RCTs E Negative evidence. Majority of RCTs show no benefit over placebo or comparator medication. F: Lack of Evidence. **Grades of recommendation:** 1: Category A plus good risk benefit ratio. 2: Category A and moderate risk-benefit ratio 3: Category B 4: Category C 5: Category D	3 Non-analytic studies eg case reports, case series 4 Expert opinion **Grades of Recommendation.** **A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+ applicable to target population and demonstrating overall consistency of results. **B** A body of evidence consisting principally of studies rated as 2++ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ **C** A body of evidence consisting principally of studies rated as 2+ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+		depend on the patient values and preferences and so more consultation should take place. System above does not apply to 2009 recommendations.	a parallel control group. Level IV: Case series with either post-test or pre-test/ post-test outcomes.

			D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+ **GPP** (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.			**D** Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+ **GPP** (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.			

Appendix 3. Comparison of recommendations from schizophrenia clinical practice guidelines. Data extracted in relation to key health questions that are relevant to a clinician adopting an algorithmic approach to the pharmacological treatment of first episode schizophrenia. Where levels of evidence or grades of recommendation were attributed to a recommendation this appears in brackets beside the recommendation. See Appendix 1 Levels of Evidence and Grades of Recommendation used in Clinical Practice Guidelines for Schizophrenia in supplementary material for further information.

	PORT, 2009	Spain, 2009	Malaysia, 2009	Singapore, 2009	BAP, 2011	WFSBP, 2012	SIGN, 2013	Harvard. 2013	NICE	RANZCP, 2016
Initial presentation										
Initial oral antipsychotic for FE (Not Cloz)	FGA or SGA. Not OLZ	SGA eg Risp, Olz, Quet, Ami, Ari (A) 24-48 hour observation period with option of BDZ (C)	SGA Ami or Olz (Grade A)	SGA or FGA (A, 1++)	SGA or FGA (A). If FGA chosen this 'should probably' be a medium or low potency drug (S).	FGA and SGA both effective (A, 1). SGA preferred (C3, 4). Level of evidence available for each antipsychotic in FE Schizophrenia tabulated. Can be assumed that other antipsychotics will work but currently no evidence to make an evidence based recommendation. Olz, Risp and Quet best SGA Hpd is only FGA with evidence (Not graded)	FGA or SGA (A) Not Cloz	SGA preferably Ami, Ari, Risp, Zip. Not Cloz, Olz, Quet	Offer oral FGA or SGA	Allow drug-free assessment with BDZ for relevant symptoms* SGA (Ami, Ari, Quet, Risp, Zip) (CBR) Not Olz
Other considerations	Not Olz due to risk of metabolic side effect.	Establish a therapeutic alliance (A)			Base choice on: Relative liability for side effects especially EPSE and metabolic problems (B) Individual patient preference (S) Individual patient risk factors from side effects (B) Relevant medical history (S)	SGA chosen because of reduced risk of neurological side effects (C3, 4). Guide treatment decision by side effect profile, individual considerations.	Healthcare professionals and service users should work together to find the most appropriate medication at lowest effective dose. Discuss potential benefit and harm. Consider service user preference (GPP) Recommendations made based on specific side effect concerns of service users: Weight Gain: Hpd, Ari, Ami (A) EPSE: SGA, low potency FGA (B) TD: SGA (B) Sedation: HPD, Ari (B)		Provide information, discuss benefits and risks. Treatment should be considered an explicit individual therapeutic trial. Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try	Olz not recommended for initial treatment for a first episode of schizophrenia Base choice on individual preference once risks and benefits have been explained, prior response, clinical response to an adequate trial, individual tolerability, potential long-term adverse effects (EBR I)

										psychological interventions alone agree a time (1 month or less) to review treatment options including antipsychotic medication.	
Dose		Start with doses lower than recommended for multi-episode schizophrenia	Low dose (B)	Lower dose	Lower end of licensed dose range (A, 1++)	Lower end of licensed dose range (A)	Lower end of standard dose range (A, 1). Evidence for this recommendation for Hpd, Olz, Risp, only. Sparse evidence for this treatment recommendation for other antipsychotics (C1/D, 4/5)	Lowest effective (D)	Minimum effective	Start at lower end of dose range and titrate up.	Lowest effective dose (EBR, II). Target doses suggested
Dose in FE	FGA	Start at 300-500 mg Cpz Eq		300-1000mg Cpz Eq (Level 1)	300-1000 Cpz Eq (A, 1++)				300-1000 mg Cpz Eq		
	Cpz		75-300mg/day								
	Sulp		400-800mg		200-400mg						
	Triflu		10mg to start		5-20mg						
	Hpd		3-9 mg daily		5-20mg		<5mg (B, 3)				
	Olz	Lower half of dose range	5-20mg/day		10-20mg		<10mg (B, 3)		10-20 mg		
	Risp	Lower half of dose range	4-6mg		2-6 mg		<4mg (B,3)		2-6 mg		2-3mg
	Arip	Insufficient evidence for recommendation	10-15mg		10-30mg				10-15 mg		15-20mg
	Quet	500- 600mg	300-450mg		300-800mg				300-750 mg		300-400mg. Rapid dose adaptation from starting dose recommended.
	Ami		400-800ng		400-800mg						300-400mg
	Palip		3-12 mg		6-10mg						
	Asen										
	Zip	Insufficient evidence for recommendation	80mg		80-160mg				160 mg (with food)		80-120mg
	Sert		12-20mg								
Duration of initial trial of antipsychotic and when to switch medication due to non-response			4-6 weeks (Not graded)	6-8 weeks (not graded)	4-6 weeks (A, 1++)	4 weeks (A)	2-8 weeks (extrapolated from the definition of TRS, not graded) Minimum of three weeks and maximum	2-4 weeks (D)	4-6 weeks	4-6 weeks	3 weeks

						of 6 weeks described in a different section (not graded)				
Duration of initial trial of antipsychotic medication trial where there is a partial response						4-10 weeks and 5-11 weeks for the second antipsychotic (not graded)	8 weeks (D)			6-8 weeks
Second line antipsychotic medication	FGA or SGA	SGA eg Risp, Olz, Quet, Ami, Ari (A)	Switching to atypical confers no advantage in terms of quality of life (Grade A).	SGA or FGA (D, 4)	SGA or FGA. Should use an AP with a favourable efficacy profile before moving to clozapine (A)	SGA if initial antipsychotic was FGA (B, 3)	FGA or SGA (extrapolated from definition of TRS)	FGA or SGA. Prefer Risp, Olz or FGA if not previously used. If one was used in initial treatment then use any AP except Cloz.	Offer oral FGA or SGA	Another SGA including option of Olz
Duration of second trial of antipsychotic medication		6-8 weeks (C) Although in the algorithm it states 4-6 weeks (not graded)	6-8 weeks (Not graded)			2-8 weeks (extrapolated from the definition of TRS, not graded) 5-11 weeks for the second antipsychotic if partial response (not graded)		4-6 weeks		
Role of long acting injection or depot antipsychotic	For maintenance treatment if preferred to oral	Reserved for those who choose this route. Those who repeatedly fail to adhere despite psychosocial and interventions aimed at adaptation and adherence (C in one section and B in another) If there is no response to treatment or low adherence with frequent relapses, low dose first generation depot antipsychotics should be tried for a period of 3-6 months (C).	If non-adherent (Grade A in one section and Grade B in another section)	If patient preference or if treatment adherence is an issue (C, 2+) Not for acute episodes because they may take 3-6 months to reach steady state (B, 2++)	Role uncertain for FE schizophrenia. Patient-specific intervention for improving adherence or if preference of patient (S)	Good evidence for FGA depots in relapse prevention (A,1) but no clear difference in efficacy between oral and depot (A,1) Good evidence for Risp LAI in relapse prevention (A,1) and some evidence of superiority over oral formulation (C,4). Also some evidence for use in FE (B,3) Evidence for Pal LAI (A,1); Olz LAI (A/B, 2/3)	Service user preference, medication adherence difficulties (B)	Not routine use. If non-adherent. Although may be necessary to ensure an adequate trial for the initial antipsychotic stage of an episode of FE schizophrenia.	Patient preference. When avoiding covert non-adherence is a clinical priority	If poor or uncertain adherence or if persons preference or poor response to oral medication (EBR II)
Combination antipsychotics		Not recommended	Monotherapy whenever	Not recommended except for switching	High dose or combined AP for	Monotherapy recommended (C3, 4)	Should not be routine. If considered	Cloz augmentation.	Do not initiate. Check PRN use of	If adequate response is not

		except when switching (B)	possible (Grade A in one section and Grade C in another) Combination with clozapine may be considered (Grade A)	or clozapine augmentation (B, 2++)-	TRS only after failure of several, adequate sequential trials of AP monotherapy and other evidence based treatments for TRS including clozapine (B). If used use a closely monitored, time-limited trial (D).	May be advisable in some individual circumstances (C3,4). Monitor at frequent intervals (C3,4) Cloz augmentation	for an individual situation, discuss benefits and harms with service user (GPP) Cloz augmentation as above	Or an option if augmentation strategies with cloz have not worked.	AP. Clozapine augmentation strategy.	achieved after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses, antipsychotic polypharmacy may be justifiable but requires careful monitoring (EBR II)
Maintenance of remission										
Duration of maintenance treatment following a first episode of schizophrenia		12 months (C)	1-2 years (not graded)			Treat for at least one year (C,4)	At least 18 months (D)		High risk of relapse if discontinued in next 1-2 years	Provide an adequate duration of treatment (EBR II) A minimum of 12 months following remission is suggested in the text (not graded). Continue to engage with first episode for schizophrenia service for at least 2-5 years (EBR II)
Choice of AP for maintenance	FGA or SGA	Continue with treatment used in acute phase (not graded).	Use AP for relapse prevention (Grade A) No difference amongst Aps in efficacy for relpse prevention (Grade A)	Same as used for acute phase (A, 1+)	Antipsychotic medication required (A) Consider factors as for first episode plus: Prior treatment response (S) Experience of side effects (S) Level of medication adherence (S). Comorbid physical illness (S) Long term treatment plan (S).	SGA because: Evidence for superiority of Risp, Olz and Sert for treatment discontinuation and relapse prevention (B,3). Reduced risk of motor side effects (C,4) Some advantage in reducing negative symptoms (C,4) Use antipsychotic with best	Offer maintenance with antipsychotic (A) Use medication that was used during acute phase assuming efficacy and tolerability (GPP) Olz, Ami, Risp preferred with CPZ and other low potency FGA an alternative (B)	Not Quet		

						benefit/tolerability profile in acute phase (Good clinical practice)				
Dose of maintenance medication following a first episode of schizophrenia (evidence from multi-episode schizophrenia)	300-600 mg Cpz Eq. SGA dose effective in acute phase			Dose should not be lower than half of the effective dose used in the acute phase (A, 1+)	Any reduction in dose should be closely monitored. Consider risk of destabilisation (C)	<600 mg Cpz Eq. FE patients require lower doses than multi-episode (C,4) Dose in accordance with stabilisation dose (C,4)	300-400 mg CPZ Eq, 4-6 mg Risp or equivalent (B)			
Targeted intermittent dosing strategies	Not recommended in preference to continuous maintenance treatment regimens due to risk of relapse.				Should not be used in preference to continued AP treatment (B).	Continuous use for relapse prevention strongly recommended (A,1). Consider if patient unwilling to accept continuous maintenance or side effect sensitivity			Not routinely. Consider if patient unwilling to accept continuous maintenance or side effect sensitivity.	
Treatment resistance										
When to offer a trial of clozapine										
If non-response following adequate trial of two AP's one of which is an SGA	Yes	Yes (A)	Yes (Grade A)	Yes (A, 1++)	Yes (A)	Yes (B,3)	Yes (B)	Yes	Yes	Yes (EBR I)
Other considerations regarding clozapine use	Trial clozapine for hostility or violent behaviour. Trial of clozapine for those who exhibit significant or persistent suicidal thoughts or behaviours.	Also indicated in persistent or high risk of suicide despite treatment for depression if present (A). SGA eg Olz and Risp trial before diagnosing TRS (C).	Clozapine superior in treating persistent aggression (Grade A) Clozapine indicated in treatment of persistent suicidal thoughts or behaviours (Grade A)		Consider trial for aggression or hostility (B). Consider if persistent substance misuse (D). Consider if intolerant to neurologic side effects of antipsychotics (A).	One SGA previously. Non response to two antipsychotics in previous 5 years. Trial at adequate dose for 2-8 weeks. (not graded) If intolerant to Cloz, try Olz or Risp (B,3). Consider Cloz if significant and continuous increased risk of suicide (B,3) Cloz may reduce craving in concurrent	One SGA in previous trial (B) If TRS accompanied by aggression/ hostility consider clozapine (D)	Previous trial of Risp, Olz or FGA More effective if presentation includes hostility and for suicide prevention.	One SGA in previous trial	When treatment resistance has been clearly demonstrated, clozapine should be offered within 6-12 months. (EBR, I) In another section an evidence level of EBR II is attached to the statement 'treatment resistant disease should be recognised within

						alcohol use disorder (B,3); and other substance use disorder (C3,4) but consider risk of non-compliance.				6-12 months of starting potentially effective antipsychotic treatment and confirmed as soon as possible.
Clozapine dose	Blood level > 350ng/ml. 300-800mg/ day	200-450mg/day		Blood level > 350ng/ml. 100-450 mg/ day (Recommendation not graded)	Plasma level can guide dose (D)	Blood level > 350ng/ml. 100-900mg/ day (B/C3; 3/4)		Blood level 350-450ng/mL Usual dose 300-400mg/day		
Adequate duration of clozapine trial?	At least 8 weeks	4-6 weeks (Not graded)			3-6 months (B)		NR			If possible a trial of clozapine should be continued for 12 months to allow for late responders (EBR I).
Clozapine augmentation strategies		Addition of a second SGA (C)	Combination with of AP clozapine may be considered (Grade A) Clozapine + ECT (Not graded)	Another AP or ECT (Recommendation not graded)	Only consider if optimised clozapine treatment for minimum of 3 months (S). Use medication that has complementary receptor profile and does not dose not compound SE (B)	Some evidence for adding SGA (C,4) Ltg augmentation might improve symptoms (B,3).	Add other SGA for trial period (C) Consider trial of Cloz + Ltg (B)	Add Risp; add other AP, LTG,	Add other AP considering SE profile	Adjunctive medication with clozapine or reinstate most efficacious previous treatment and add adjunctive medication (EBR II).
Duration of trial of augmentation strategy?					At least 10 weeks (B)		10 weeks for augmentation with SGA (C)		8-10 weeks	
High dose antipsychotics					Not recommended unless all evidence based treatments for TRS have been optimised and failed. Time limited trial (B) Continue after 3 months only if benefit outweighs risk (S).	Not recommended (not graded)	Trial if clozapine and augmentation strategies have failed (D). Need to develop local guidelines for monitoring (GPP)	Not recommended	Do not use loading dose. Caution with additional PRN AP's	

Unsatisfactory improvement despite clozapine augmentation			Information appears in algorithm not in main text and is not graded. AP combinations, AP + ECT, AP + mood stabiliser.	AP combinations AP + ECT AP plus another augmenting agent e.g. mood stabiliser. (Recommendation not graded)		Inconsistent evidence for memantine in TRS (D,5)		Options presented below. Note sparce evidence. Not listed in order of preference. Try a different clozapine augmentation strategy. Add mementine or omega 3 fatty acid to clozapine. Stop cloz and try AP not previously tried. Stop Cloz. Try combination of FGA and mirtazapine or celecoxib. Try combinations of AP not including cloz.		

Abbreviations: AP= Antipsychotic; CPZ Eq = Chlorpromazine Equivalents; ECT = electroconvulsive therapy; EPSE = Extrapyramidal side effects; FE = First Episode; FGA = First generation antipsychotic; LAI = Long Acting Injection; PRN = 'Pro re nata' as required; SE = side effect; SGA = Second generation antipsychotic; TD = Tardive Dyskinesia; TRS = Treatment resistant schizophrenia

Medications: Ami= Amisulpride; Ari = Aripiprazole; BDZ = Benzodiazepine; Cloz = clozapine; CPZ = chlorpromazine; Hpd = haloperidol; Olz = Olanzapine; Palip= Paliperidone; Quet = Quetiapine; Risp = Risperidone; Sert= sertindole; Sulp= sulpiride; Triflu = trifluperazine; Zip = ziprasidone

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and Supplemantary material 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemantary material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 and Supplemantary material 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9,12

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 19
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013881.R1
Article Type:	Research
Date Submitted by the Author:	10-Nov-2016
Complete List of Authors:	Keating, Dolores; Pharmacy Department; Royal College of Surgeons in Ireland, School of Pharmacy McWilliams, Stephen; Saint John of God Hospital Schneider, Ian; Saint James's Hospital Hynes, Caroline; Saint John of God Hospital Cousins, Gráinne; Royal College of Surgeons in Ireland, School of Pharmacy Strawbridge, Judith; Royal College of Surgeons in Ireland, School of Pharmacy Clarke, Mary; DETECT Early Intervention in Psychosis Service
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Medical management, Pharmacology and therapeutics, Evidence based practice
Keywords:	Schizophrenia & psychotic disorders < PSYCHIATRY, psychosis, antipsychotic, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode.

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Word Count (excluding title, abstract, figures and tables):

4487

ABSTRACT

Objectives

Clinical practice guidelines (CPGs) support the translation of research evidence into clinical practice. Key health questions in CPGs ensure that recommendations will be applicable to the clinical context in which the guideline is used. The objectives of this study were to identify CPGs for the pharmacological treatment of first-episode schizophrenia; assess the quality of these guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument; and compare recommendations in relation to the key health questions that are relevant to the pharmacological treatment of first-episode schizophrenia.

Methods

A multidisciplinary group identified key health questions that are relevant to the pharmacological treatment of first-episode schizophrenia. The MEDLINE and Embase databases, websites of professional organisations and international guideline repositories were searched for CPGs that met the inclusion criteria. The AGREE II instrument was applied by three raters and data extracted from the guidelines in relation to the key health questions.

Results

In total, 3299 records were screened. Ten guidelines met the inclusion and exclusion criteria. Three guidelines scored well across all domains. Recommendations varied in specificity. Side effect concerns, rather than comparative efficacy benefits, were a key consideration in antipsychotic choice. Antipsychotic medication is recommended for maintenance of remission following a first episode of schizophrenia but there is a paucity of evidence to guide duration of treatment. Clozapine is universally regarded as the medication of choice for treatment resistance. There is less evidence to guide care for those who do not respond to clozapine.

Conclusions

An individual's experience of using antipsychotic medication for the initial treatment of first-episode schizophrenia may have implications for future engagement, adherence and outcome. While guidelines of good quality exist to assist in medicines optimisation, the evidence base required to answer key health questions relevant to the pharmacological treatment of first-episode schizophrenia is limited.

KEY WORDS

Guideline, schizophrenia, psychosis, antipsychotic.

Strengths and limitations of the study

- This is the first study to assess the quality of guidelines applicable to the pharmacological treatment of first-episode schizophrenia.
- A multidisciplinary group identified key health questions that informed a clinically focussed, systematic approach to data extraction to enhance the relevance for medicines optimisation.
- Robust application of a validated tool (AGREE II) to assess the quality of clinical practice guidelines for the pharmacological treatment of first-episode schizophrenia.
- A limitation of the study is that only guidelines written in English were included.
- The application of the AGREE II instrument reflects the quality of guideline reporting which may not always indicate all information about how the guideline was developed.

INTRODUCTION

Schizophrenia is a complex mental illness that has a significant impact on the individual and their families. The lifetime risk of schizophrenia is approximately 1% and typically manifests in early adulthood.[1] The disorder is characterised by positive symptoms (such as delusions, hallucinations and disorganised speech), negative symptoms (such as social withdrawal and reduced motivation) and cognitive impairment.[2] Approximately three quarters of people who have been diagnosed with schizophrenia will experience a relapse with about one fifth going on to have long term symptoms and disability.[1 3] The life expectancy of people with schizophrenia is reduced by 15-20 years compared to those without severe mental ill-health, only 8% are in employment and the cost to society in England is estimated at £11.8 billion per year.[4]

In recent years there has been an increasing emphasis on early intervention for people experiencing psychotic symptoms and on the reduction of the duration of untreated psychosis.[5] Comprehensive programmes for the treatment of first-episode schizophrenia aim to promote recovery, improve quality of life and functional outcomes.[6] Antipsychotic medication is a key component of the treatment offered but the clinical use of these medicines differs in the management of first-episode schizophrenia in comparison to a relapse or recurrence of an established illness.[7] At first presentation, a positive experience of using medication is likely to have long term implications for adherence and outcome.[8]

Medicines optimisation is described as by the National Institute for Health and Care Excellence as a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines.[9] To promote medicines optimisation, we must ensure that

an individualised, evidence informed choice of medication is made available to service users.[9] Translating the best available evidence into practice is a challenge so Clinical Practice Guidelines (CPGs) are a useful summary of the most recent thinking in an area of clinical medicine. The Institute of Medicine describes CPGs as "*statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*".[10] Guidelines and algorithms in mental health care can improve the quality of the services offered and the safety of medication use.[11 12] Key health questions are used in guideline development processes to clarify the scope and purpose of the individual guideline.[13 14] The definition of a set of clear and focussed health questions will ensure that the recommendations are applicable to the clinical context in which the guideline is intended to be used.[14]

The quality of guidelines will have an impact on their applicability. The AGREE II tool has been used as a way of assessing the quality of guideline reporting in healthcare.[15-18] A systematic review and critical appraisal of guidelines for the treatment of schizophrenia was carried out by Gaebel *et al* in 2005.[15] At this time Gaebel *et al* did not include the pharmacological treatment of first-episode schizophrenia when comparing the guidelines. Gaebel and colleagues updated this work in 2011 by reviewing the most recent versions of CPGs that were considered to be of good quality in 2005.[16] Differences in treatment recommendations have been evaluated by various authors in relation to guidelines that apply to the United States,[19] or the difference in recommendations for single aspects of care such as maintenance treatment.[20] As guidelines are updated or new guidelines become available it is important to continue to assess their quality and understand how the growing evidence base has influenced recommendations.

The aim of this paper is to review the quality of CPGs and compare guideline recommendations to inform practice in the field of first-episode schizophrenia. We sought to do this by adopting a systematic approach to retrieving relevant guidelines; using AGREE II to assess the quality of guidelines; developing a list of key health questions relevant to the pharmacological treatment of first-episode schizophrenia and comparing guideline recommendations in relation to the key health questions identified.

METHODOLOGY

Data sources and search strategy

The PubMed and Embase databases were searched for guidelines relating to the pharmacological treatment of first-episode schizophrenia (search terms described in Supplementary Material,

Appendix 1). A number of guideline repositories and specialist websites were searched for relevant guidelines. A hand search of reference lists for all identified guidelines was conducted. The initial search was conducted for guidelines published between January 2009 and April 2016.

Inclusion and exclusion criteria

Guidelines were included if they contained recommendations about the pharmacological treatment of adults experiencing a first episode of schizophrenia. A multidisciplinary group, comprising consultant psychiatrists, pharmacists and nurses, with expertise in the care of people experiencing a first episode of schizophrenia, identified key clinical questions that a clinician would consider when taking an algorithmic approach to the use of medication for adults presenting with a first episode of schizophrenia (Table 1). These key questions then informed the selection of guidelines to be included in the analysis.

Guidelines were included if they were written in English, and made treatment recommendations based on a systematic review of the evidence in relation to adults of 18 years or older. One reviewer (DK) did an initial screen of titles and abstracts to identify potentially eligible records. Two reviewers (DK and SMcW) then completed the second screen of abstracts to identify records that would undergo full review. Where more than one record related to a single guideline development process, they were considered together.

Table 1: Key health questions in an algorithmic approach to the pharmacological treatment of the positive symptoms of schizophrenia in adults presenting to an early intervention for psychosis service.

Initial presentation

- Which antipsychotic medications should be offered for the initial management of positive symptoms associated with a first episode of schizophrenia?
- What is the recommended dose of antipsychotic medications for first-episode schizophrenia?
- What is the duration of an initial trial of an antipsychotic for people experiencing a first episode of schizophrenia?
- Which antipsychotic medication should be considered when the person has not responded to the initial antipsychotic trialled?
- How long should a second antipsychotic trial last following non-response to the initial antipsychotic medication?
- Is there a role for long acting injectable antipsychotic medications or depot antipsychotic formulations in the management of first-episode schizophrenia?
- When are combinations of antipsychotic medication an appropriate treatment strategy for people experiencing a first episode of schizophrenia?

Maintenance of remission

- Which antipsychotic medication is recommended for the maintenance of remission from positive symptoms following a first episode of schizophrenia?
- What is the dose of maintenance antipsychotic medication following a first episode of psychosis?
- What is the duration of maintenance treatment following a first episode of schizophrenia?
- Can targeted intermittent treatment with antipsychotic medication be recommended in the management of first-episode schizophrenia?

Treatment resistance

- When should clozapine be considered in the pharmacological management of first-episode schizophrenia?
- What is the recommended dose of clozapine?
- What is the recommended duration of a clozapine trial to adequately assess response?
- What strategies can be recommended for people who have had an inadequate response to clozapine treatment?

Assessment of guideline quality

The AGREE II instrument contains 23 items grouped into 6 domains; scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence.[13] The items are rated from 1 (strongly disagree) to 7 (strongly agree). Domain scores are then scaled between 0% and 100%. Following completion of the online AGREE II tutorial and practice exercise,[21] three reviewers (DK, SMcW, IS) independently applied the AGREE II criteria to each guideline. Domain scores were calculated based on the sum of all ratings within the domain and scaled by including the minimum possible score and the difference between the maximum and minimum possible scores for that domain.[21] The AGREEII score calculator from McMaster University was used to calculate the domain scores and assess inter-rater reliability.[22] A low level of discrepancy between raters (less than 1.5 standard deviations from the mean domain score) was found for each of the six domains within each guideline. The raters used the domain scores to judge overall acceptability of the guidelines for the purpose of informing the pharmacological treatment of first-episode schizophrenia.

Comparison of guideline recommendations

Data in relation to guideline recommendations for the key health questions (table 1) were extracted by one reviewer (DK) and then a second reviewer (CH) checked the accuracy of this work.

RESULTS

Search and selection of guidelines

The search strategy identified a total of 3299 records which were screened and yielded a final number of 10 guidelines for inclusion in the analysis (Figure 1). The guidelines and their general characteristics are listed in table 2. The guideline from the World Journal for the Society of Biological Psychiatrists (WFSBP) is published in three parts but considered as one guideline.[23-25] The Royal Australia and New Zealand College of Psychiatrists (RANZCP) guideline,[26] cross references an Australian guide for the medical management of early psychosis,[27] and they are therefore considered together. The reasons for excluding guidelines included lack of documented development methodology, language other than English, that the guideline was entirely based on another guideline or that it did not address the pharmacological treatment of first-episode schizophrenia.

Table 2: General characteristics of guidelines for the pharmacological treatment of first-episode schizophrenia.

Title	Author/ Institution	Country	Publication Date	End of Search Date *	Abbreviation and Reference
The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements	Schizophrenia Patient Outcomes Research Team	USA	December 2009	March 2008	PORT,[28]
Clinical Practice Guidelines for Schizophrenia and Incipient Psychotic Disorder	Ministry of Health and Consumer Affairs	Spain	March 2009	July 2007	Spain,[29]
Management of Schizophrenia in Adults	Ministry of Health, Malaysia	Malaysia	May 2009	Not described	Malaysia,[30]
Schizophrenia Clinical Practice Guidelines	Ministry of Health. Singapore	Singapore	April 2011	Not Described	Singapore,[31]
Evidence- based guidelines for the pharmacological treatment of schizophrenia: recommendations form the British Association for Clinical Psychopharmacology	British Association for Clinical Psychopharmacology	UK	2011	September 2008	BAP,[32]
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia	World Federation of Societies of Biological Psychiatry (WFSBP)	International	May 2012 to March 2015	March 2012	WFSBP,[23-25]
Management of Schizophrenia	Scottish Intercollegiate Guidelines Network	Scotland	March 2013	December 2011	SIGN,[3]
The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Schizophrenia	Harvard Medical School	USA	January 2013	Not described. Paper submitted for publication December 2011	Harvard,[33]
Psychosis and schizophrenia in adults: treatment and management	National Institute for Health and Clinical Excellence	UK	February 2014	December 2008 (for pharmacological treatment)	NICE,[34]
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the	Royal Australian and New Zealand College of Psychiatrists	Australia and New Zealand	2014 and 2016	Not described	RANZCP,[26 27]

management of schizophrenia and related disorders					
*Final search date of the systematic review of evidence that informed the guideline development process.					

Assessment of Guideline Quality

The standardised domain scores for each CPG are detailed in Table 3. The domain scores for 'Scope and purpose' were generally high with all but one guideline,[33], scoring greater than 80% (range 50-100%). There was wider variation among domain scores for stakeholder involvement ranging from 20% to 90%. The reporting of development methodology as assessed by the 'rigor of development' domain was of variable quality with a range of 41% to 91%. In the domain 'clarity of presentation' CPGs generally scored well (range 52% to 96%) in contrast to the 'applicability' domain which had wide variability (14% to 79%). The reporting of 'editorial independence' in CPGs was scored between 25% and 86%. The guidelines selected were generally of good quality with 3 guidelines recommended for use as written, 6 guidelines acceptable with modifications and one not recommended. All reviewers were in agreement with overall guideline acceptability.

Table 3: Domain scores for clinical practice guidelines (CPG) addressing the pharmacological treatment of first-episode schizophrenia using AGREE II as assessed by three raters and scaled as a percentage of the maximum possible score for each domain.

Domain	PORT (%)	Spain (%)	Malaysia (%)	Singapore (%)	BAP (%)	WFSBP (%)	SIGN (%)	Harvard (%)	NICE (%)	RANZCP (%)
Scope and Purpose	85	85	100	96	93	83	96	50	100	81
Stakeholder Involvement	54	80	93	75	63	44	90	20	89	67
Rigour of Development	69	82	74	41	56	61	91	57	84	49
Clarity of Presentation	85	89	94	94	83	52	96	78	94	83
Applicability	29	57	39	40	38	21	79	14	75	31
Editorial Independence	78	75	97	25	39	64	78	86	86	42
Overall assessment	Y	Y	Y/M	N	Y/M	Y/M	Y	Y/M	Y	Y/M
Y = Guideline is recommended for use; Y/M = Guideline is acceptable with modifications; N = Guideline is not recommended.										

Comparison of clinical practice guideline (CPG) content

Rating the quality of evidence used to support recommendations.

Guideline development groups had a range of approaches to rating the quality of the evidence and grading the strength of related recommendations. The methodologies used are listed in the supplemental material (Supplemental Material, Appendix 2). One CPG did not describe a method for grading evidence.[33] PORT took a very direct approach of needing two randomised controlled trials (RCTs) as the minimum level of evidence required to make a recommendation.[28] NICE requires the reader to understand the language used within the recommendations to interpret the strength of the recommendation.[34] Other groups used methods of varying detail and complexity to describe the strength of evidence.[3 23 26 29-32]

Recommendations in relation to key health questions at initial presentation

A table comparing the recommendation from CPGs in relation to key health questions is available in the supplementary material, Appendix 3. Guidelines broadly agree that all antipsychotics are equally effective for the treatment of positive symptoms in first-episode schizophrenia. [3 23 26 28-34] There is also a consensus that the most important consideration when helping a person make a decision about pharmacological treatment is the side effect profile of the antipsychotic. [3 23 26 28-34] Five guidelines recommend second generation antipsychotic (SGA) medications as the preferred initial choice because of the view that the side effect profiles of this group of medicines is more favourable.[23 26 29 30 33] Olanzapine is specifically excluded as a recommended initial choice of antipsychotic medication from PORT,[28] Harvard,[33] and RANZCP,[26] because of the issue of metabolic side effects and weight gain. Harvard uses the additional consideration of efficacy in the maintenance phase of treatment in excluding quetiapine because of a poorer evidence base for maintenance of remission.[33] All guideline development groups consider the evidence for the use of antipsychotic medications for first-episode schizophrenia to be of high quality even though not all antipsychotic medication have been tested in this cohort of patients. For example WFSBP notes that haloperidol is the only first generation antipsychotic (FGA) that has actually been used in trials in first-episode schizophrenia.[23] Spain,[29] and RANZCP,[26] recommend an antipsychotic free assessment period using benzodiazepines to help alleviate distress.

The most common recommendation for the duration of an initial trial of antipsychotic medication is 4 weeks.[29 31-34] Evidence that the majority of the benefit seen with antipsychotic medication will be apparent in the first two weeks of treatment is reflected in the potentially shorter trial period

suggested by some guidelines.[3 23 26] There is consensus regarding the lowest effective dose being used with a number of guidelines offering suggestions for FGA and SGA doses specific to the first episode of schizophrenia.[23 26 28 33] The only exception to this dose recommendation is that of quetiapine, which requires a dose similar to that used in acute relapse based on the interpretation of the European First Episode Study (EUFEST),[35] trial by PORT.[28]

Oral medication is recommended with parenteral formulations reserved for those who prefer this route of administration or when poor adherence is a clinical priority. [3 23 26 28-34] While monotherapy is ideal there is recognition that combinations of antipsychotic medication may be useful in certain scenarios such as clozapine augmentation. [3 23 26 28-34]

Recommendations in relation to key health questions regarding the maintenance of remission following a first episode of schizophrenia.

Recommendations regarding the duration of maintenance treatment following a first episode of schizophrenia vary between one and two years,[3 24 26 29 30 34] with some guideline development groups failing to make any recommendation.[28 31-33] RANZCP considers engagement with a first-episode schizophrenia service for up to five years to be beneficial.[26] The antipsychotic medication used for relapse prevention is generally the antipsychotic used in the acute management of symptoms at the dose that was effective in the acute phase.[3 24 28-31 33] Evidence for the superiority of medications such as olanzapine and risperidone or inferiority of quetiapine in relapse prevention is reflected in the recommendations of some guidelines.[3 24 33] Targeted, intermittent treatment is a potential strategy that reduces side effect burden and the need for adherence to longer term medication use. The evidence, however, does not support this approach because of the increased risk of relapse in comparison to continuous treatment.[24 28 32 34]

Recommendations in relation to key health questions regarding treatment resistant schizophrenia

There is consensus that the definition of treatment resistance is the failure of two trials of antipsychotic medication at optimal dose for an adequate period of time.[3 23 26 28-34] Before making a diagnosis of treatment resistance additional considerations include co-morbid substance misuse and an assessment of treatment adherence. The interpretation of recent evidence regarding the efficacy of antipsychotic medication,[36] points to the trial of olanzapine, risperidone or amisulpride as one of the two antipsychotics used before a trial of clozapine is considered.[3 33] Clozapine is universally recommended as the treatment of choice for treatment resistant schizophrenia. The variation in

doses suggested reflect the individuality of clozapine use in clinical practice, [24 28 29 31-33] with the potential for delayed response to clozapine treatment leading to the longer duration of a trial of clozapine of up to one year recommended in some guidelines.[26 28 29 32] The most common strategy suggested when there has been a partial response to clozapine despite dose optimisation is to combine clozapine with a second antipsychotic taking additional side effect profile and pharmacology into consideration.[3 24 26 29-34] Lamotrigine is also considered by some CPGs to have sufficient evidence to recommend its use as a clozapine augmentation strategy.[3 24 33] There is very little evidence to guide treatment options for those who do not have adequate symptom reduction despite clozapine augmentation.[24 30 31 33]

DISCUSSION

Assessment of Guideline Quality

This systematic review identified ten CPGs addressing the pharmacological management of first-episode schizophrenia which were assessed using the AGREE II instrument. The NICE, SIGN and Spanish guidelines scored best across all domains.[3 29 34] The CPGs assessed were generally well presented with specific statements describing the scope and purpose of each guideline. The 'rigor of development' scores for each guideline reflected the quality of methodological reporting within the text of the guideline. Plans to update the guidelines were documented for 6 of the CPGs.[3 28-31 34] Updates are currently due for two guidelines.[29 30] The majority of recommendations regarding the pharmacological treatment of first-episode schizophrenia in the NICE guidelines have not been updated since the 2009 version of the CPG.[34] In most guidelines there is significant cross referencing of other similar guidelines.[3 23 29-32] SIGN and Malaysia used the NICE evidence base as their foundation.[3 30] This would appear reasonable as the NICE guideline was considered of very high quality in Gaebel *et al's* systematic review.[15]

Guidelines were generally weakest in the applicability domain with little offered by way of support for implementation. Examples of tools used to support applicability included versions of the CPG for service users,[3 29 34] algorithms,[26 29 33 34] and quality indicators.[30 34] The inclusion of tools such as decision aids in guidelines may improve their applicability and make a collaborative approach to care more feasible in clinical practice.[37 38] Overall assessment of quality was lowest for guidelines produced by specialist organisations, where limited stakeholder involvement added to poor applicability,[23 32 33] or the reporting of development methodology was limited.[23 26 33] Within the evidence base itself, publication bias is an important consideration.[39 40] CPGs such as NICE and SIGN make significant efforts to measure the risk of bias in original trials.[3 34] Response and remission are not well defined in the guidelines even though some recommend using rating scales to assess same.

Evidence-based recommendations are drawn up following an evaluation of available research and ranked according to the strength of the supporting evidence. Consensus based recommendations are derived from the practical experience of the guideline developers. This methodology allows for the development of recommendations for clinical scenarios where the published evidence is weak or the evidence doesn't reflect the patient characteristics of everyday clinical practice.[41] While the 'rigor of development' domain scores may be excellent in an AGREE assessment, the specificity of the subsequent recommendations vary. NICE emphasise that each treatment phase be considered an individual therapeutic trial and that this will encompass any new evidence that is published in relation to pharmacological approaches.[34] In contrast, the WFSBP guideline evaluates the evidence in relation to each antipsychotic medication and Harvard makes more specific recommendations regarding the choice of antipsychotic medication.[23 33] It is clear from the levels of evidence used to make recommendations in CPGs that the available research is not comprehensive enough to address all key health questions relevant to the pharmacological treatment of first-episode schizophrenia. It is therefore reasonable to accept a transparent, consensus-based approach so that the reader can also take a view on the topic.

Clinical Significance

Early intervention for those experiencing their first episode of schizophrenia has the potential to improve outcomes and is an important area of current research.[42-45] Early intervention services provide a range of pharmacological, psychological and educational interventions with the aims of symptom remission and functional recovery with respect to personal, employment, educational and social outcomes.[46] Antipsychotic medication is a key component of care.[6] The clinical use of medication differs in this cohort of patients, who tend to be more sensitive to the effects of antipsychotic medication and more vulnerable to adverse effects than those in later phases of the illness.[35] Specific guidelines that address the key health questions relevant to the pharmacological treatment of first-episode schizophrenia are therefore required.

Navigating the varying side effect profiles of individual antipsychotic medicines has become the clinical priority when choosing the most appropriate medication in first-episode schizophrenia. Adverse effects have a significant impact on quality of life and adherence to medication,[47 48] and this must be balanced against the fact that residual symptoms also have an impact on quality of life.[49] Research among those experiencing their first episode of schizophrenia demonstrated the increased

sensitivity to metabolic side effects of SGAs without greater efficacy when compared to FGAs.[35 50] The risk of long term neurological side effects such as tardive dyskinesia with FGAs has led to a consensus among some guideline development groups that SGAs are preferable in first-episode schizophrenia.[23 26 29 30 33] Where FGAs are chosen, low potency FGAs such as chlorpromazine are preferred. [3 23 32] Guidelines that relegate olanzapine to second line treatment do so because of the relatively high risk of metabolic side effects and weight gain in particular.[26 28 33] An antipsychotic free assessment period is recommend by two CPGs, presumably to allow for a clear picture of symptoms to be obtained at baseline.[26 29] However, the feasibility of implementing this recommendation depends on ease of access to specialised assessments for first-episode schizophrenia and it may not be reasonable to delay treatment.

Approximately 20% of those who meet the diagnostic criteria for a first episode of schizophrenia will not go on to experience any subsequent episodes.[1] The optimal duration of treatment following a first episode of schizophrenia is therefore an important health question. In one recent study the relapse rate for those who discontinued medication following 18 months of treatment (and were in clinical remission for more than 12 months with 6 months or more of functional recovery) was twice that of those who continued maintenance antipsychotic medication over the three year study period.[51] There is evidence of benefit for service users who remain in contact with an early intervention service for up to 5 years compared to those who do not.[42] Wunderink and colleagues have suggested that shorter periods of antipsychotic use should be used, arguing that despite reoccurrence of symptoms, quality of life at seven year follow up was better for those who had discontinued medication at six months than those who received maintenance antipsychotic medication.[52] These findings have not been replicated and current practice supports maintenance treatment with informed choices to be made at an individual level regarding continuation of antipsychotic medication at approximately two years following symptom remission of the first episode.[53]

Evaluations of the efficacy of antipsychotic medication have not demonstrated superiority for any individual agent for those experiencing a first episode of schizophrenia,[34] with response rates between 40% and 90%.[54] Clozapine, for example, is no more effective than chlorpromazine as initial treatment.[55] Response rates to a subsequent trials of antipsychotic medications other than clozapine are poor.[56] Recent evidence suggests that there may be some efficacy benefit for individual SGAs in the acute phase of established recurrent schizophrenia[36] and for maintenance of remission.[57] This evidence has been interpreted in guidelines by suggesting that risperidone, olanzapine or amisulpride should be used as one of the two antipsychotics recommended before a trial of clozapine is considered.[3 33] While oral medication is recommended in CPGs, there is increasing

interest in the use of long acting antipsychotic injections early in schizophrenia treatment because of the potential to detect non-adherence early, reduce relapse and improve psychosocial functioning.[58]

Clozapine is universally accepted by guideline development groups as the antipsychotic of choice for treatment resistant schizophrenia. Approximately 60% of those who are considered treatment resistant will respond to clozapine.[59] Leucht *et al's* analysis of the efficacy of antipsychotic medication in the acute phase of multi-episode schizophrenia showed the relative benefit of clozapine.[36] The use of clozapine is supported by open label studies, cohort studies and database studies with important positive outcomes such as reduced hospitalisation.[60-62] However, in a recent multivariate meta-analysis of randomised controlled trials comparing clozapine and other antipsychotic medication, the Cochrane Collaboration failed to find any significant efficacy difference in treatment resistant schizophrenia.[63] The authors highlighted the many limitations of RCTs in the area of treatment resistance including varying definitions of treatment resistance, dose of antipsychotics and the difficulty of blinding to clozapine treatment. Given the benefits of clozapine for treatment resistant schizophrenia and the importance of early effective treatment for those experiencing a first episode of schizophrenia, it has been argued that clozapine should be considered earlier in the treatment algorithm as a second line option.[54]

CPGs are not intended to dictate all aspects of care for patients. Individual factors such as personal preferences, co-morbidity, concurrent medications, and previous experience with medication will have an impact on the choices made. Although guidelines and algorithms in mental health care can improve the quality of medication use,[11 12] CPGs are not always used in practice[64-66] and implementation strategies do not always result in improved adherence to guideline recommendations.[67] In the Recovery After an Initial Schizophrenia Episode (RAISE) study, the authors identified 39% of the sample who could have benefitted from a medication review because prescribing practices were not in line with current guidelines in the United States.[68] For example, the use of olanzapine was relatively high even though it is specifically not recommended in a first episode of schizophrenia by the PORT guidelines. The UK National Audit of Schizophrenia examined the implementation of NICE guidelines. While most of the sample of 5608 patients were receiving pharmacological treatment in line with the guideline, 11% were prescribed two or more antipsychotic medications and 10% were prescribed doses above the recommended limits.[69] Despite the importance placed on early use of clozapine in CPGs, evidence suggests it is under-prescribed with many different strategies being used before clozapine is offered.[70 71] Clozapine's effectiveness may diminish if used later in the illness making it vitally important to identify treatment resistance and manage it appropriately as early as possible.[72] Within the setting of an early intervention service it may be feasible to implement guidelines more effectively when they are relevant to those

experiencing a first episode of schizophrenia, are facilitated by local buy-in, and reflect a multidisciplinary approach.[64]

Strengths and Limitations

The clinical use of antipsychotic medication as part of the early intervention model of service delivery is an important topic of current research. A strength of this study is the identification of key health questions that are relevant to clinical practice and the comparison of guideline recommendations in relation to these key health questions. The AGREE II tool has been extensively used to evaluate the quality of CPGs in many aspects of clinical care including psychiatry.[15 17 18] Using the AGREE II tool helps to identify guidelines that have a transparent, systematic method of development. For services that are not bound by national guidelines, this work could inform the development of local guidelines using methodology such as the ADAPTE process.[14]

The AGREE II tool does not evaluate the quality of the evidence that was used to formulate the recommendations. The subjectivity inherent in the application of the AGREE II tool is reduced by the independent scoring of CPGs by three raters and by further measuring any marked discrepancy between scores. While every effort was made to include all relevant guidelines for the treatment of first-episode schizophrenia, it is possible that some have been inadvertently excluded. We only included guidelines written in the English language. Many of the guidelines included were published more than five years ago and could therefore be considered out of date[10]. A comparison of CPG content would ideally involve taking the various methods by which quality of evidence is evaluated and grouping them into one standard method.[14] The AGREE tool includes an assessment of bias in relation to statements of conflict of interest for those involved in guideline development and stakeholder involvement. Even if conflicts of interest were declared, it was difficult to ascertain how this was managed and how it influenced final recommendations.[73] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group have developed an Evidence to Decision (EtD) framework for CPGs that has the potential to ensure a structured, transparent approach to developing CPG recommendations.[74]

CONCLUSIONS

The aims of early intervention for those experiencing a first episode of schizophrenia are to reduce symptoms and improve outcomes. Optimal use of antipsychotic medication is critical and clinical practice differs for the first-episode cohort in comparison to those experiencing multi-episode

schizophrenia. CPGs can guide medicines optimisation but it is important for the target uses to assess the quality of CPGs so that they can have confidence in the recommendations made. The AGREE II instrument is a useful way of structuring this assessment. CPGs of good methodological quality for the pharmacological treatment of first-episode schizophrenia exist but deficiencies in the evidence base make it difficult to address the key health questions relevant to medicines optimisation in clinical practice. Further research is required to guide choice and dose of medication, duration of treatment, and the management of treatment resistance.

CONTRIBUTIONS

DK developed the concept. DK, GC and SMcW contributed to the search for data. DK, SMcW and IS were involved in the application of the AGREE II tool. DK and CH participated in the extraction of data. JS and MC participated in substantive review of the manuscript.

COMPETING INTERESTS

The authors report no competing interests

FUNDING

This research received no specific financial support.

DATA SHARING STATEMENT

No additional data available

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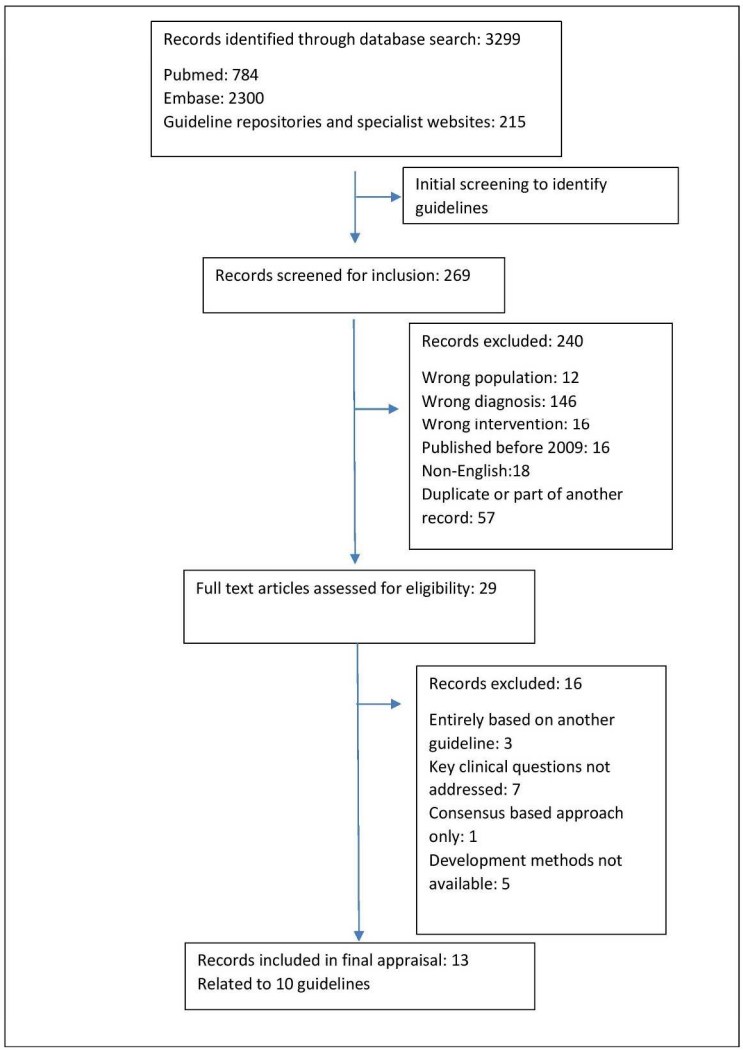

Figure 1. PRISMA diagram describing process of guideline selection.

579x822mm (96 x 96 DPI)

Appendix 1. Search terms and search strategy

The search terms used for PubMed were "Psychotropic Drugs"[Mesh], "antipsychotic"[All Fields], "antipsychotics"[All Fields] "guideline"[Publication Type] "guidelines as topic"[MeSH Terms], "guidelines"[All Fields]), "guideline"[All Fields], "consensus development conference"[Publication Type] "consensus development conferences as topic"[MeSH Terms]"consensus"[All Fields] "recommend"[All Fields] "recommends"[All Fields] "recommendation"[All Fields], "recommendations"[All Fields], "Schizophrenia and Disorders with Psychotic Features"[Mesh], "schizophrenia"[All Fields], "schizophrenic"[All Fields], "schizophreniform"[All Fields] "psychosis"[All Fields], "psychotic"[All Fields], "schizoaffective"[All Fields]

The search terms used for Embase were "schizophrenia"[All Fields], "schizophrenic"[All Fields], "schizophreniform"[All Fields] "psychosis"[All Fields], "psychotic"[All Fields], "schizoaffective"[All Fields], 'schizophrenia'/exp, 'psychotropic agent'/exp, "antipsychotic"[All Fields], "antipsychotics"[All Fields], 'practice guideline'/exp, "guideline"[All Fields], "guidelines"[All Fields] "consensus"[All Fields] "recommend"[All Fields] "recommends"[All Fields] "recommendation"[All Fields], "recommendations"[All Fields],

The guideline repositories searched were the Guidelines International Network, National Guidelines Clearing House, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, Canadian Medical Association Infobase, British Columbia Ministry of Health, Australian National Health and Medical Research Council, Australian Government clinical Practice Guidelines Portal, New Zealand Guidelines Group, German National Disease Management Guideline Programme.

The specialist association websites searched were; Canadian Psychiatric Association, Canadian agency for Drugs and Technology in Health, Substance Abuse and Mental Health Services, Administration, American Psychiatric Association, Veterans Affairs United States, World Society of Biological Psychiatry, Australia and New Zealand Psychiatric Association, European Psychiatric Association, International Psychopharmacology Algorithm Project, British Association for Psychopharmacology, Texas Medication Algorithm Project, world Psychiatric Association, International Early Psychosis Association, Early Psychosis Prevention and Intervention Centre, Lambeth Early Onset Services, Early Detection and Treatment of Psychosis (TIPS) Norway, Prevention and Early Intervention for Psychosis Programme Canada, South London and Maudsley NHS Trust Prescribing Guidelines.

Appendix 2: Levels of evidence and grades of recommendation used to describe the strength of recommendations in clinical practice guidelines (CPG) addressing the pharmacological treatment of first episode schizophrenia.

PORT 2009	Spain 2009	Malaysia, 2009	Singapore 2011	BAP 2011	WFSBP, 2012	SIGN, 2013	Hayward 2013	NICE 2014	RANZCP, 2016
Must have at least 2 RCTs to make a recommendation	Ia Meta-analysis of RCTs Ib At least one RCT IIa At least one well designed non-randomised controlled prospective study IIb At least one well designed quasi-experimental study III Well designed observational studies eg comparative study, correlation study or case-control studies IV Expert opinion and clinical experience Grade A: Evidence level 1a or 1b. At least one good quality RCT. Grade B: Evidence level IIa, IIb, or III. Methodologically correct clinical trials that are not RCTs Grade C: Evidence level IV. Expert opinion in the absence of other clinical evidence.	Level 1, good strength, Meta-analysis of RCT, systematic review. Level 2, good strength. Large sample RCT Level 3, Good to fair strength. Small sample RCT. Level 4, Good to fair strength. Non-randomised controlled prospective trial. Level 5, fair strength. Non-randomised controlled prospective trial with historical control. Level 6. Fair strength. Cohort study. Level 7, Poor strength, case-controlled study. Level 8, Poor strength, Non-controlled clinical series, descriptive studies multi-centre Level 9, poor strength, Expert committees, consensus, case reports, anecdotes.	1++ High quality meta- analysis, systematic reviews of RCTs or RCT with very low risk of bias. 1+ Well-conducted meta-analysis, systematic reviews of RCTs or RCTS with a low risk of bias 1- Meta-analysis, systematic reviews of RCTs or RCTs with a high risk of bias 2++ High quality systematic reviews of case control or cohort studies, High quality case control or cohort studies with a very low risk of bias or confounding and a high probability that the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of bias or confounding and a moderate probability that the relationship is causal. 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.	***Causal relationships and treatment*** Category I; Meta-analysis of RCTs, at least one large good quality RCT or replicated, smaller RCTs. Category II: Small non-replicated RCT; at least one controlled study or at least one other quasi experimental study. RCT must have a control treatment arm. Category III: non-experimental descriptive studies eg comparative, correlation or case control. Category (IV) Expert committee report/ opinion/ clinical experience ***Non-causal relationships*** Category I: Evidence from large representative population samples. Category II: Evidence from small, well-designed, but not necessarily representative samples.	Category of Evidence: A: Full evidence from controlled studies: Two or more double blind RCT vs placebo and one or more RCT vs active comparator with placebo arm or well conducted non-inferiority trial. If there is an existing negative study it must be outweighed by at least 2 positive studies or a meta-analysis. B: Limited positive evidence from controlled studies. One or more RCT showing superiority to placebo or RCT vs comparator without placebo control and no negative studies exist. C Evidence from Uncontrolled studies/ case reports/ expert opinion. C1: Uncontrolled studies: 1 or more positive naturalistic study, comparison with an existing drug with sufficient sample size and no negative studies. C2: Case reports. One or more positive case	1++ High quality meta- analysis, systematic reviews of RCTs or RCT with very low risk of bias. 1+ Well-conducted meta-analysis, systematic reviews of RCTs or RCTS with a low risk of bias 1- Meta-analysis, systematic reviews of RCTs or RCTs with a high risk of bias 2++ High quality systematic reviews of case control or cohort studies, High quality case control or cohort studies with a very low risk of bias or confounding and a high probability that the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of bias or confounding and a moderate probability that the relationship is causal. 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.	None described	Strength of recommendation described in the language of the recommendation. <u>Must or must not</u>: Legal duty to apply recommendation of if consequences of not following recommendation are serious or life threatening. <u>Should or should not:</u> Indicates a strong recommendation. 'Offer', 'refer', 'advise' when confident that for the vast majority of patients an intervention will do more good than harm and be cost effective. Conversely 'do not offer' when confident that intervention will not be of benefit for most patients. <u>Could be used.</u> 'Consider' if confident that an intervention will do more good than harm for most patients, be cost effective but other options may be similarly cost effective. Choice of the intervention more likely to	Recommendations are either Evidence based (EBR) or consensus based (CBR). The level of evidence on which EBR is according to the National Health and Medical Research Council's levels of evidence for healthcare interventions. Level I: A systematic review of level II studies. Level II: A randomised controlled trial. Level III-1: A pseudo-randomised controlled trial. Level III-2: A comparative study with concurrent controls: non-randomised, experimental trial. Cohort studies. Case-control study. Interrupted time-series with a control group. Level III-3: A comparative study without concurrent controls. Historical control study. Two or more single-arm studies. Interrupted time series without

		Grades of Recommendation. A. At least one meta-analysis, systematic review, RCT, or evidence rated as good and directly applicable to the target population. B. Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review, or RCT. C. Evidence from expert committee reports, or opinions and/or clinical experiences of related authorities; indicates absence of directly applicable clinical studies of good quality.	3 Non-analytic studies eg case reports, case series 4 Expert opinion **Grades of Recommendation.** **A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+ applicable to target population and demonstrating overall consistency of results. **B** A body of evidence consisting principally of studies rated as 2++ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ **C** A body of evidence consisting principally of studies rated as 2+ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+	Category III: Evidence from non-representative surveys, case reports. Category IV: Evidence from expert committee reports or opinions and /or clinical opinions of respected authorities. ***Strength of recommendation*** A: Category I B Category II or extrapolated from category I C: Category III or extrapolated from category I or II D: Category IV or extrapolated from category I, II or III S: Standard of good practice	reports. No negative controlled studies. C3: Expert opinion or clinical experience. D: Inconsistent results. Equal number of positive and negative RCTs E Negative evidence. Majority of RCTs show no benefit over placebo or comparator medication. F: Lack of Evidence. **Grades of recommendation:** 1: Category A plus good risk benefit ratio. 2: Category A and moderate risk-benefit ratio 3: Category B 4: Category C 5: Category D	3 Non-analytic studies eg case reports, case series 4 Expert opinion **Grades of Recommendation.** **A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+ applicable to target population and demonstrating overall consistency of results. **B** A body of evidence consisting principally of studies rated as 2++ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ **C** A body of evidence consisting principally of studies rated as 2+ applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+		depend on the patient values and preferences and so more consultation should take place. System above does not apply to 2009 recommendations.	a parallel control group. Level IV: Case series with either post-test or pre-test/ post-test outcomes.

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			D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+ **GPP** (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.			**D** Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+ **GPP** (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.			

Appendix 3. Comparison of recommendations from schizophrenia clinical practice guidelines. Data extracted in relation to key health questions that are relevant to a clinician adopting an algorithmic approach to the pharmacological treatment of first episode schizophrenia. Where levels of evidence or grades of recommendation were attributed to a recommendation this appears in brackets beside the recommendation. See Appendix 1 Levels of Evidence and Grades of Recommendation used in Clinical Practice Guidelines for Schizophrenia in supplementary material for further information.

	PORT, 2009	Spain, 2009	Malaysia, 2009	Singapore, 2009	BAP, 2011	WFSBP, 2012	SIGN, 2013	Harvard. 2013	NICE	RANZCP, 2016
Initial presentation										
Initial oral antipsychotic for FE (Not Cloz)	FGA or SGA. Not OLZ	SGA eg Risp, Olz, Quet, Ami, Ari (A) 24-48 hour observation period with option of BDZ (C)	SGA Ami or Olz (Grade A)	SGA or FGA (A, 1++)	SGA or FGA (A). If FGA chosen this 'should probably' be a medium or low potency drug (S).	FGA and SGA both effective (A, 1). SGA preferred (C3, 4). Level of evidence available for each antipsychotic in FE Schizophrenia tabulated. Can be assumed that other antipsychotics will work but currently no evidence to make an evidence based recommendation. Olz, Risp and Quet best SGA Hpd is only FGA with evidence (Not graded)	FGA or SGA (A) Not Cloz	SGA preferably Ami, Ari, Risp, Zip. Not Cloz, Olz, Quet	Offer oral FGA or SGA	Allow drug-free assessment with BDZ for relevant symptoms* SGA (Ami, Ari, Quet, Risp, Zip) (CBR) Not Olz
Other considerations	Not Olz due to risk of metabolic side effect.	Establish a therapeutic alliance (A)			Base choice on: Relative liability for side effects especially EPSE and metabolic problems (B) Individual patient preference (S) Individual patient risk factors from side effects (B) Relevant medical history (S)	SGA chosen because of reduced risk of neurological side effects (C3, 4). Guide treatment decision by side effect profile, individual considerations.	Healthcare professionals and service users should work together to find the most appropriate medication at lowest effective dose. Discuss potential benefit and harm. Consider service user preference (GRC) Recommendations made based on specific side effect concerns of service users: Weight Gain: Hpd, Ari, Ami (A) EPSE: SGA, low potency FGA (B) TD: SGA (B) Sedation: HPD, Ari (B)		Provide information, discuss benefits and risks. Treatment should be considered an explicit individual therapeutic trial. Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try	Olz not recommended for initial treatment for a first episode of schizophrenia Base choice on individual preference once risks and benefits have been explained, prior response, clinical response to an adequate trial, individual tolerability, potential long-term adverse effects (EBR I)

										psychological interventions alone agree a time (1 month or less) to review treatment options including antipsychotic medication.	
Dose		Start with doses lower than recommended for multi-episode schizophrenia	Low dose (B)	Lower dose	Lower end of licensed dose range (A, 1++)	Lower end of licensed dose range (A)	Lower end of standard dose range (A, 1). Evidence for this recommendation for Hpd, Olz, Risp, only. Sparse evidence for this treatment recommendation for other antipsychotics (C1/D, 4/5)	Lowest effective (D)	Minimum effective	Start at lower end of dose range and titrate up.	Lowest effective dose (EBR, II). Target doses suggested
Dose in FE	FGA	Start at 300-500 mg Cpz Eq		300-1000mg Cpz Eq (Level 1)	300-1000 Cpz Eq (A, 1++)				300-1000 mg Cpz Eq		
	Cpz		75-300mg/day								
	Sulp		400-800mg		200-400mg						
	Triflu		10mg to start		5-20mg						
	Hpd		3-9 mg daily		5-20mg		<5mg (B, 3)				
	Olz	Lower half of dose range	5-20mg/day		10-20mg		<10mg (B, 3)		10-20 mg		
	Risp	Lower half of dose range	4-6mg		2-6 mg		<4mg (B,3)		2-6 mg		2-3mg
	Arip	Insufficient evidence for recommendation	10-15mg		10-30mg				10-15 mg		15-20mg
	Quet	500- 600mg	300-450mg		300-800mg				300-750 mg		300-400mg. Rapid dose adaptation from starting dose recommended.
	Ami		400-800ng		400-800mg						300-400mg
	Palip		3-12 mg		6-10mg						
	Asen										
	Zip	Insufficient evidence for recommendation	80mg		80-160mg				160 mg (with food)		80-120mg
	Sert		12-20mg								
Duration of initial trial of antipsychotic and when to switch medication due to non-response			4-6 weeks (Not graded)	6-8 weeks (not graded)	4-6 weeks (A, 1++)	4 weeks (A)	2-8 weeks (extrapolated from the definition of TRS, not graded) Minimum of three weeks and maximum	2-4 weeks (D)	4-6 weeks	4-6 weeks	3 weeks

						of 6 weeks described in a different section (not graded)				
Duration of initial trial of antipsychotic medication trial where there is a partial response						4-10 weeks and 5-11 weeks for the second antipsychotic (not graded)	8 weeks (D)			6-8 weeks
Second line antipsychotic medication	FGA or SGA	SGA eg Risp, Olz, Quet, Ami, Ari (A)	Switching to atypical confers no advantage in terms of quality of life (Grade A).	SGA or FGA (D, 4)	SGA or FGA. Should use an AP with a favourable efficacy profile before moving to clozapine (A)	SGA if initial antipsychotic was FGA (B, 3)	FGA or SGA (extrapolated from definition of TRS)	FGA or SGA. Prefer Risp, Olz or FGA if not previously used. If one was used in initial treatment then use any AP except Cloz.	Offer oral FGA or SGA	Another SGA including option of Olz
Duration of second trial of antipsychotic medication		6-8 weeks (C) Although in the algorithm it states 4-6 weeks (not graded)	6-8 weeks (Not graded)			2-8 weeks (extrapolated from the definition of TRS, not graded) 5-11 weeks for the second antipsychotic if partial response (not graded)		4-6 weeks		
Role of long acting injection or depot antipsychotic	For maintenance treatment if preferred to oral	Reserved for those who choose this route. Those who repeatedly fail to adhere despite psychosocial and interventions aimed at adaptation and adherence (C in one section and B in another) If there is no response to treatment or low adherence with frequent relapses, low dose first generation depot antipsychotics should be tried for a period of 3-6 months (C).	If non-adherent (Grade A in one section and Grade B in another section)	If patient preference or if treatment adherence is an issue (C, 2+) Not for acute episodes because they may take 3-6 months to reach steady state (B, 2++)	Role uncertain for FE schizophrenia. Patient-specific intervention for improving adherence or if preference of patient (S)	Good evidence for FGA depots in relapse prevention (A,1) but no clear difference in efficacy between oral and depot (A,1) Good evidence for Risp LAI in relapse prevention (A,1) and some evidence of superiority over oral formulation (C,4). Also some evidence for use in FE (B,3) Evidence for Pal LAI (A,1); Olz LAI (A/B, 2/3)	Service user preference, medication adherence difficulties (B)	Not routine use. If non-adherent. Although may be necessary to ensure an adequate trial for the initial antipsychotic stage of an episode of FE schizophrenia.	Patient preference. When avoiding covert non-adherence is a clinical priority	If poor or uncertain adherence or if persons preference or poor response to oral medication (EBR II)
Combination antipsychotics		Not recommended	Monotherapy whenever	Not recommended except for switching	High dose or combined AP for	Monotherapy recommended (C3, 4)	Should not be routine. If considered	Cloz augmentation.	Do not initiate. Check PRN use of	If adequate response is not

		except when switching (B)	possible (Grade A in one section and Grade C in another) Combination with clozapine may be considered (Grade A)	or clozapine augmentation (B, 2++)-	TRS only after failure of several, adequate sequential trials of AP monotherapy and other evidence based treatments for TRS including clozapine (B). If used use a closely monitored, time-limited trial (D).	May be advisable in some individual circumstances (C3,4). Monitor at frequent intervals (C3,4) Cloz augmentation	for an individual situation, discuss benefits and harms with service user (GPP) Cloz augmentation as above	Or an option if augmentation strategies with cloz have not worked.	AP. Clozapine augmentation strategy.	achieved after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses, antipsychotic polypharmacy may be justifiable but requires careful monitoring (EBR II)
Maintenance of remission										
Duration of maintenance treatment following a first episode of schizophrenia		12 months (C)	1-2 years (not graded)			Treat for at least one year (C,4)	At least 18 months (D)		High risk of relapse if discontinued in next 1-2 years	Provide an adequate duration of treatment (EBR II) A minimum of 12 months following remission is suggested in the text (not graded). Continue to engage with first episode for schizophrenia service for at least 2-5 years (EBR II)
Choice of AP for maintenance	FGA or SGA	Continue with treatment used in acute phase (not graded).	Use AP for relapse prevention (Grade A) No difference amongst Aps in efficacy for relpse prevention (Grade A)	Same as used for acute phase (A, 1+)	Antipsychotic medication required (A) Consider factors as for first episode plus: Prior treatment response (S) Experience of side effects (S) Level of medication adherence (S). Comorbid physical illness (S) Long term treatment plan (S).	SGA because: Evidence for superiority of Risp, Olz and Sert for treatment discontinuation and relapse prevention (B,3). Reduced risk of motor side effects (C,4) Some advantage in reducing negative symptoms (C,4) Use antipsychotic with best	Offer maintenance with antipsychotic (A) Use medication that was used during acute phase assuming efficacy and tolerability (GPP) Olz, Ami, Risp preferred with PPZ and other low potency FGA as alternative (B)	Not Quet		

						benefit/tolerability profile in acute phase (Good clinical practice)				
Dose of maintenance medication following a first episode of schizophrenia (evidence from multi-episode schizophrenia)	300-600 mg Cpz Eq. SGA dose effective in acute phase			Dose should not be lower than half of the effective dose used in the acute phase (A, 1+)	Any reduction in dose should be closely monitored. Consider risk of destabilisation (C)	<600 mg Cpz Eq. FE patients require lower doses than multi-episode (C,4) Dose in accordance with stabilisation dose (C,4)	300-400 mg CPZ Eq, 4-6 mg Risp or equivalent (B)			
Targeted intermittent dosing strategies	Not recommended in preference to continuous maintenance treatment regimens due to risk of relapse.				Should not be used in preference to continued AP treatment (B).	Continuous use for relapse prevention strongly recommended (A,1). Consider if patient unwilling to accept continuous maintenance or side effect sensitivity			Not routinely. Consider if patient unwilling to accept continuous maintenance or side effect sensitivity.	
Treatment resistance										
When to offer a trial of clozapine										
If non-response following adequate trial of two AP's one of which is an SGA	Yes	Yes (A)	Yes (Grade A)	Yes (A, 1++)	Yes (A)	Yes (B,3)	Yes (B)	Yes	Yes	Yes (EBR I)
Other considerations regarding clozapine use	Trial clozapine for hostility or violent behaviour. Trial of clozapine for those who exhibit significant or persistent suicidal thoughts or behaviours.	Also indicated in persistent or high risk of suicide despite treatment for depression if present (A). SGA eg Olz and Risp trial before diagnosing TRS (C).	Clozapine superior in treating persistent aggression (Grade A) Clozapine indicated in treatment of persistent suicidal thoughts or behaviours (Grade A)		Consider trial for aggression or hostility (B). Consider if persistent substance misuse (D). Consider if intolerant to neurologic side effects of antipsychotics (A).	One SGA previously. Non response to two antipsychotics in previous 5 years. Trial at adequate dose for 2-8 weeks. (not graded) If intolerant to Cloz, try Olz or Risp (B,3). Consider Cloz if significant and continuous increased risk of suicide (B,3) Cloz may reduce craving in concurrent	One SGA in previous trial (B) If TRS accompanied by aggression/ hostility consider clozapine (D)	Previous trial of Risp, Olz or FGA More effective if presentation includes hostility and for suicide prevention.	One SGA in previous trial	When treatment resistance has been clearly demonstrated, clozapine should be offered within 6-12 months. (EBR, I) In another section an evidence level of EBR II is attached to the statement 'treatment resistant disease should be recognised within

						alcohol use disorder (B,3); and other substance use disorder (C3,4) but consider risk of non-compliance.				6-12 months of starting potentially effective antipsychotic treatment and confirmed as soon as possible.
Clozapine dose	Blood level > 350ng/ml. 300-800mg/ day	200-450mg/day		Blood level > 350ng/ml. 100-450 mg/ day (Recommendation not graded)	Plasma level can guide dose (D)	Blood level > 350ng/ml. 100-900mg/ day (B/C3; 3/4)		Blood level 350-450ng/mL Usual dose 300-400mg/day		
Adequate duration of clozapine trial?	At least 8 weeks	4-6 weeks (Not graded)			3-6 months (B)		NR			If possible a trial of clozapine should be continued for 12 months to allow for late responders (EBR I).
Clozapine augmentation strategies		Addition of a second SGA (C)	Combination with of AP clozapine may be considered (Grade A) Clozapine + ECT (Not graded)	Another AP or ECT (Recommendation not graded)	Only consider if optimised clozapine treatment for minimum of 3 months (S). Use medication that has complementary receptor profile and does not dose not compound SE (B)	Some evidence for adding SGA (C,4) Ltg augmentation might improve symptoms (B,3).	Add other SGA for trial period (C) Consider trial of Cloz + Ltg (B)	Add Risp; add other AP, LTG,	Add other AP considering SE profile	Adjunctive medication with clozapine or reinstate most efficacious previous treatment and add adjunctive medication (EBR II).
Duration of trial of augmentation strategy?					At least 10 weeks (B)		10 weeks for augmentation with SGA (C)		8-10 weeks	
High dose antipsychotics					Not recommended unless all evidence based treatments for TRS have been optimised and failed. Time limited trial (B) Continue after 3 months only if benefit outweighs risk (S).	Not recommended (not graded)	Trial if clozapine and augmentation strategies have failed (D). Need to develop local guidelines for monitoring (GPP)	Not recommended	Do not use loading dose. Caution with additional PRN AP's	

Unsatisfactory improvement despite clozapine augmentation			Information appears in algorithm not in main text and is not graded. AP combinations, AP + ECT, AP + mood stabiliser.	AP combinations AP + ECT AP plus another augmenting agent e.g. mood stabiliser. (Recommendation not graded)		Inconsistent evidence for memantine in TRS (D,5)		Options presented below. Note sparce evidence. Not listed in order of preference. Try a different clozapine augmentation strategy. Add mementine or omega 3 fatty acid to clozapine. Stop cloz and try AP not previously tried. Stop Cloz. Try combination of FGA and mirtazapine or celecoxib. Try combinations of AP not including cloz.		

Abbreviations: AP= Antipsychotic; CPZ Eq = Chlorpromazine Equivalents; ECT = electroconvulsive therapy; EPSE = Extrapyramidal side effects; FE = First Episode; FGA = First generation antipsychotic; LAI = Long Acting Injection; PRN = 'Pro re nata' as required; SE = side effect; SGA = Second generation antipsychotic; TD = Tardive Dyskinesia; TRS = Treatment resistant schizophrenia

Medications: Ami= Amisulpride; Ari = Aripiprazole; BDZ = Benzodiazepine; Cloz = clozapine; CPZ = chlorpromazine; Hpd = haloperidol; Olz = Olanzapine; Palip= Paliperidone; Quet = Quetiapine; Risp = Risperidone; Sert= sertindole; Sulp= sulpiride; Triflu = trifluperazine; Zip = ziprasidone

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and Supplemantary material 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemantary material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 and Supplemantary material 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9,12

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 19
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist