Treatment of schizotypal disorder: a protocol for a systematic review of the evidence and recommendations for clinical practice

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ABSTRACT

Introduction Schizotypal disorder is associated with a high level of disability at an individual level and high societal costs. However, clinical recommendations for the treatment of schizotypal disorder are scarce and based on limited evidence. This review aims to synthesise the current evidence on treatment for schizotypal disorder making recommendations for clinical practice.

Methods and analysis This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic literature search will be performed in PsychArticles, Embase, Medline and Cochrane Central Register of Controlled Trials. Additionally, we will search for relevant articles manually. Inclusion criteria are published studies including individuals diagnosed with schizotypal personality disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, or schizotypal disorder according to International Classification of Diseases (ICD) criteria. We will include interventional studies comprising any pharmacological and non-pharmacological treatment trials for patients with schizotypal disorder, and all relevant outcome measures will be reported. Risk of bias will be assessed by Cochrane risk-of-bias tools. Data will be synthesised using narrative or thematic analysis and, if suitable, through meta-analysis.

Ethics and dissemination No original data will be collected as part of this study and ethics approval is, therefore, not applicable. The results will be disseminated through peer-reviewed publication and presented at international scientific meetings. We will aim at submitting the final paper for publication within 4 months of completion of analyses. Furthermore, this systematic review will inform clinicians and researchers on the current state of evidence on treatment for schizotypal disorder. Findings may guide proposals for further research and potentially guide recommendations for clinical practice using the Grading of Recommendations Assessment, Development and Evaluation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We aim to create the most comprehensive systematic review on the effectiveness of treatment for schizotypal disorder by including all intervention studies on treatment with a targeted sample comprising patients with schizotypal disorder exclusively, creating a more homogeneous sample.

⇒ The methodology used is in accordance with the Cochrane guidelines and the results will be reported as stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

⇒ The search algorithm will be customised to four large databases as well as including papers found through handsearch.

⇒ Only articles written in English will be included.

INTRODUCTION

Background

The clinical diagnosis of schizotypal disorder comprises patients with relatively mild schizophrenia-spectrum psychopathology and is historically linked with the notion of schizophrenia as a developmental disorder. Thus, already Kraepelin and Bleuler, who first described the clinical entity of schizophrenia, remarked that mild features of this illness could be observed in relatives of patients.1,2 Before the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (1980), several overlapping diagnostic categories (such as latent schizophrenia, borderline schizophrenia and pseudoneurotic schizophrenia) were used for patients with schizophrenia-spectrum psychopathology below the diagnostic threshold of schizophrenia.3 Rado and Meehl argued for the notion of a schizophrenia spectrum4,5 as a continuum from compensated subclinical cases to clinical pseudoneurotic schizophrenia (ie, schizotypal disorder) to schizophrenia proper with manifest psychosis. Rado coined the term ‘schizotypy’ for a postulated constitution underlying these varying degrees of clinical symptomatic manifestation. The schizophrenia-spectrum concept was subsequently empirically validated in
narrowed family studies (for a review, see Parnas et al). It is compatible with a diathesis-stress model emphasising an interplay between innate (genetic) and environmental influences.

The creation of the DSM-III criteria of schizotypal personality disorder (STPD) (unchanged in subsequent version of the DSM and largely identical with the International Classification of Diseases, Tenth Revision (ICD-10) criteria) was based on the clinical descriptions of ‘borderline’ and ‘pseudoneurotic schizophrenia’. In the ICD-10, schizotypal disorder is placed in a joint diagnostic category with schizophrenia, whereas the corresponding DSM-5 diagnosis of STPD is listed as a personality disorder, as well as in the section on schizophrenia and other psychotic disorders. Due to duration criteria of a minimum of 2 years of symptoms (ICD-10) or ‘an enduring pattern of symptoms that are relatively stable over time’ (DSM-5) a certain persistence of the symptomatology is implicit to the diagnosis. The diagnostic criteria for STPD in DSM-5 consists of ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences and bodily illusions, odd thinking and speech, suspiciousness or paranoid ideation, inappropriate or constricted affect, behaviour or appearance that is odd, eccentric, or peculiar, lack of close friends or confidants, other than first-degree relatives, and excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears. In this paper, we will use schizotypal disorder as an overall term referring to both schizotypal disorder in the ICD and STPD in DSM.

As a clinical category, historically linked with a developmental perspective on schizophrenia, schizotypal disorder is related to current notions in ultra- or schizotypal disorder in the ICD and STPD in DSM. Schizotypal disorder as an overall term referring to both schizotypal disorder and schizophrenia, whereas the corresponding DSM-5 diagnosis of STPD is listed as a personality disorder, as well as in the section on schizophrenia and other psychotic disorders. Due to duration criteria of a minimum of 2 years of symptoms (ICD-10) or ‘an enduring pattern of symptoms that are relatively stable over time’ (DSM-5) a certain persistence of the symptomatology is implicit to the diagnosis. The diagnostic criteria for STPD in DSM-5 consists of ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences and bodily illusions, odd thinking and speech, suspiciousness or paranoid ideation, inappropriate or constricted affect, behaviour or appearance that is odd, eccentric, or peculiar, lack of close friends or confidants, other than first-degree relatives, and excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears. In this paper, we will use schizotypal disorder as an overall term referring to both schizotypal disorder in the ICD and STPD in DSM.

A clinical category, historically linked with a developmental perspective on schizophrenia, schizotypal disorder is related to current notions in ultra-high-risk (UHR) or clinical high risk (CHR) research. Thus, studies have reported 25%–35% transition rates from schizotypal disorder to schizophrenia-spectrum psychosis. However, the criteria for UHR and CHR states emphasise state rather than persistent psychopathology features, which are implicit to the diagnosis of schizotypal disorder. Moreover, negative and disorganised symptoms are de-emphasised in UHR and CHR criteria. Notably, the importance of understanding the continuum of schizotypal disorder and these related at-risk states to improve early detection and treatment has been emphasised. Currently, more evidence is needed regarding disability, prevalence and clinical trajectories of non-transitioned individuals with UHR/CHR state and schizotypal disorder. Categorising schizotypal disorder as a prodromal state of psychosis may possibly negatively impact the treatment offered to patients with schizotypal disorder. For example, viewing the conditions as a prodromal state may miss taking the trait-like features of the disorders into account. Additionally, a substantial amount of research is dedicated to discovering variables predicting transition from schizotypal disorder or a clinical high-risk state to psychosis, but research on treatment of schizotypal disorder as a separate diagnosis is scarce. Also, patients with schizotypal disorder may vary greatly in constellation of symptom as both attenuated psychotic symptoms, self-disorders and comorbid symptoms from other mental disorders often is included in the broader clinical picture. This complexity may lead to a low detection rate, schizotypal disorder being misdiagnosed and leading to complications in treatment planning. Hence, there is a need for defining and treating schizotypal disorder as a separate diagnosis.

This is also reflected in the finding that no evidence-based recommendations for treatment of schizotypal disorder exist and the international and national guidelines for treating schizophrenia spectrum disorders do not discuss treatment of schizotypal disorder separately. Furthermore, guidelines for the treatment of personality disorders pay little attention to schizotypal disorder. Due to the possible negative consequences of schizotypal disorder (e.g., impaired real-world functioning, cognitive impairment and high disability), both at an individual and at societal level, this is a point of concern.

The prevalence of schizotypal disorder has been described as ranging from 0.6% in a Norwegian population to 4.6% in an American population with significantly higher rates among men than in women. Schizotypal disorder as a distinct diagnosis is associated with considerable use of mental health services and with great disability, even when controlling for sociodemographic parameters and comorbid disorders. According to a study by Hastrup et al, the social cost of schizotypal disorder is greater than that for borderline personality disorder and approximately the same as that of patients with schizophrenia with €47 215 per year shared between lost productivity, healthcare costs and home care costs. Furthermore, the social costs were found the be increased 5 years before initial diagnosis. A study by McClure et al found impaired real-world functioning in patients with schizotypal disorder with the additional finding of patients with schizotypal disorder being more likely to live alone and earn a lower wage than healthy controls. Cognitive impairment is seen as a manifestation of schizotypal disorder. Studies have found multiple areas of cognitive deficits in patients with schizotypal disorder, but that the degree of impairments are lower than that seen in patients with schizophrenia. Selected findings on impairments are found in the domains of attention-shifting, working-memory, empathy-related social cognition and difficulties in context-processing and mentalising, including theory-of-mind deficits.

Taken together, these findings point towards essential deficits in cognition and social and occupational functioning in this population, which underscores the need for developing targeted, evidence-based treatments for the disorder.

**Aim**

The objective of this systematic review is to synthesise research on effective treatments for schizotypal disorder making recommendations for clinical practice. We will incorporate evidence from medical, psychological and
psychosocial interventions on symptom reduction for patients with schizotypal disorder.

**METHODS**

The systematic review protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols checklist. The PICO model (Patient/Population, Intervention, Comparison and Outcomes) has been used to define focused clinical questions.

**Preliminary search**

We have searched PROSPERO, Cochrane Library, Medline and Google Scholar for reviews on this topic (from July 2022 to September 2022). The search revealed one existing protocol for a systematic review on psychological and psychosocial interventions to increase quality of life in patients with schizophrenia and related disorders. The published review could not be located after searching in relevant databases. We found two systematic reviews addressing treatment of schizotypal disorder, and one review addressing challenges associated with treating schizotypal disorder. One systematic review investigated antipsychotic treatment for schizotypal disorder, but only searched for articles in PubMed and Embase from the period 1972 to 2012. Additionally, a review by Bellino et al investigated approaches to pharmacotherapy for personality disorders and separated findings on schizotypal disorder from other personality disorders.

To the best of our knowledge, no existing systematic reviews on the topic have been published after Kirchner et al. Their final search was performed on 14 September 2016. Furthermore, this review only included interventions on medication and psychotherapy, and included studies of mixed populations with both schizotypal disorder and borderline disorder. This review will give an updated overview on all treatment modalities of schizotypal disorder, and propose clinical treatment guidelines based on an overview of evidence on wide treatment options, such as psychotherapy, psychosocial interventions and medication.

**Eligibility criteria**

Eligible studies include (1) human patients at any age, (2) that have been diagnosed with STPD according to DSM criteria or schizotypal disorder according to ICD-10 criteria. As there have not been any changes in DSM diagnostic criteria of STPD since DSM-III, we will include studies using the three latest versions of the manual. (3) Studies must include a treatment intervention for STPD/ schizotypal disorder. Any treatment intervention will be included, for example, medical, psychosocial and therapeutic interventions.

There are no restrictions on reported outcome measures as we wish to capture all relevant studies aimed at treating schizotypal disorder. There are no restrictions on time of publication as we aim to capture a broader set of treatment options than previous reviews on the topic.

This systematic review excludes all studies not meeting criteria for STPD/schizotypal disorder, including studies with patients diagnosed with schizophrenia (eg, schizophrenia, schizophreniform disorder, schizoaffective disorder). Studies including patients meeting UHR for psychosis criteria, without stratification based on schizotypal disorder, will also be excluded. Additionally, we will exclude non-peer-reviewed articles, articles not published in English, conference abstracts, current opinion articles, letters to editor and other articles not reporting primary studies and single case studies.

**Search strategy**

We will use the following databases: PsychArticles, Embase, Medline and Cochrane Central Register of Controlled Trials (CENTRAL). We will use medical subject headings (MeSH) in Medline and CENTRAL, Thesaurus terms in PsychArticles and Emtree subject headings in Embase. No date limits will be imposed on the search. We will use non-classified terms for searching titles, keywords and abstracts. The search method will be block search. Overview of full search strategy in Medline is presented in online supplemental appendix 1. We will also search for relevant articles using handsearching to identify relevant articles not found by electronic search due to non-existent, inaccurate, or incomplete indexing, and to locate articles outside of the chosen databases. Handsearching will be performed by reading reference lists of studies found through the systematic search as well as the preliminary search through already published reviews on the topic.

**Study selection**

Title and abstract will be screened to detect potential studies meeting the eligibility criteria, followed by full-text screening to assess suitability for inclusion. Screening of studies will be done by two researchers independently. All discrepancies will be resolved in collaboration or by a third author.

**Outcomes**

No specific outcome is imposed on the search to access as many articles as possible. This review will define the outcome as defined by the specific study. We expect that there will be only few studies investigating treatment effect for schizotypal disorder. Therefore, no outcome is placed on the search to collect as many relevant studies as possible. We anticipate most studies to define primary outcome as symptom levels as rated on The Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) or other relevant measurement tools, cognitive functioning, quality of life or whether the patient meets diagnostic criteria for schizotypal disorder or not.
Data management and quality assessment

We will use Covidence to manage data throughout the review. Articles will be transferred to Covidence directly from the databases. We will use Covidence for the first stage selection of studies based on title, keywords, and abstract and second stage selection based on full-text screening. Covidence will also be used for data extraction.

Data synthesis

We will qualitatively synthesise results of single studies. If results of selected studies are sufficient and suitable, we will synthesise results using random effects meta-analysis. Meta-analyses will be done using Review Manager (RevMan) software V.5.4.38 We will model heterogeneity using subgroup analysis. Studies are defined as sufficient and suitable for meta-analysis if two or more studies investigate the effect of the same intervention on the same primary outcome, both studies report the correct data needed to perform a meta-analysis (ie, means and SDs), as well as level of heterogeneity between the studies are at a minimum. We will report results not suitable for meta-analysis using narrative or thematic synthesis. We will consider heterogeneity when interpreting results.

We plan to conduct the following subgroup analyses:

► Analyse different types of interventions separately.
► Analyse diagnosis according to DSM or ICD separately.
► Compare men and woman in relation to the effect of treatment.
► Compare high risk of bias studies with low risk of bias studies.

Assessment of risk of heterogeneity

For studies available for meta-analysis, we will assess statistical heterogeneity using I². We will define substantial heterogeneity as an I² > 60%. If enough studies are available, subgroup analysis will be used to explore possible variables explaining statistical heterogeneity. The analysis will be performed in RevMan.38

Assessment of review quality

Confidence in cumulative evidence will be discussed based on possible limitations and strengths of included studies using Grading of Recommendations Assessment, Development and Evaluation (GRADE).39 Clinical practice recommendations will be based on the accumulation of evidence found for each intervention separately, the characteristics of the field these recommendations are proposed for, and the relationship between desirable and undesirable consequences of an intervention.40

If any deviation from review protocol, this will be clearly stated at submission of the review.

Assessment of risk of bias

Risk of bias assessment will be done by two reviewers independently. All discrepancies will be solved through discussion or with a third reviewer. We will assess risk of bias in each individual study using Risk Of Bias In Non-randomised Studies—of Interventions41 as we anticipate most studies to fall into this category. Risk of bias

Data extraction

We will extract data using the data extraction template 2.0 in Covidence.37 As we will include articles with different study designs, we will edit the template accordingly. Data will be extracted by two review authors independently. Any disagreement will be resolved by discussion or by a third reviewer. Extracted study characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overview of study characteristics extracted from included studies</th>
</tr>
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<tbody>
<tr>
<td>General information</td>
<td>Study ID&lt;br&gt;Title&lt;br&gt;Lead author contact details&lt;br&gt;Country in which the study was conducted&lt;br&gt;Year of publication</td>
</tr>
<tr>
<td>Methods</td>
<td>Aim of study&lt;br&gt;Study design&lt;br&gt;Start and end date&lt;br&gt;Study funding sources&lt;br&gt;Conflicts of interest for trial authors</td>
</tr>
<tr>
<td>Participants</td>
<td>Population description (eg, inpatients or outpatients)&lt;br&gt;Diagnosis according to DSM or ICD criteria&lt;br&gt;Recruitment method&lt;br&gt;Sample size&lt;br&gt;Sex&lt;br&gt;Age&lt;br&gt;Inclusion criteria&lt;br&gt;Exclusion criteria&lt;br&gt;Comorbid conditions&lt;br&gt;Drop-out rate/number lost to follow-up and their reasons</td>
</tr>
<tr>
<td>Interventions</td>
<td>Type of intervention (ie, psychotherapy, medicine, social interventions)&lt;br&gt;The number, duration and frequency of intervention&lt;br&gt;Adherence to intervention (ie, mean percentage of therapy sessions attended)&lt;br&gt;Concomitant treatments</td>
</tr>
<tr>
<td>Comparators</td>
<td>Type of comparator&lt;br&gt;Dosage if reported psychopharmacological treatment&lt;br&gt;Duration of treatment</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary and secondary outcomes reported by the study authors&lt;br&gt;Methods for outcome measurement (ie, self-report, clinical interview)&lt;br&gt;Time points for outcome measurement&lt;br&gt;Effect measures reported by the study authors on effect of intervention</td>
</tr>
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DSM, The Diagnostic and Statistical Manual of Mental Disorders; ICD, The International Classification of Diseases.
in randomised controlled trials will be assessed using a revised tool to assess risk of bias in randomised trials (RoB 2). We will assess each domain as low risk of bias, high risk of bias or unclear/some concerns. If all criteria are assessed as low risk of bias, we will code the study as overall low risk of bias. If one domain is assessed as high risk of bias or uncertain/some concerns, we will code the study as overall high risk of bias or uncertain/some concerns, respectively.

Possible publication bias will be investigated using funnel plots for each intervention separately. Publication bias will only be addressed when 10 or more studies present data on the same intervention due to a minimum of 10 studies being recommended to ensure the strength of indication.

Ethics and dissemination
No original data will be collected as part of this study and ethics approval is therefore not applicable. The results will be disseminated through peer-reviewed publication and presented at international scientific meetings. We will aim at submitting the final paper for publication within 4 months of completion of analyses. Furthermore, this systematic review will inform clinicians and researchers on the current state of evidence on treatment for schizotypal disorder. Findings may guide proposals for further research and, potentially, guide recommendations for clinical practice using GRADE.

Patient and public involvement
Patients or the public have not been involved in the design, conduct, reporting or dissemination plans of the study.

DISCUSSION
This systematic review will provide an updated overview of available treatment options for patients with schizotypal disorder along with the current evidence for the use of different forms of treatment that may possibly provide clinical recommendations based on GRADE. This is highly needed as there is a lack of evidence-based recommendations for treatment of schizotypal disorder.

This systematic review has several strengths. We have included a broad range of treatment options and does not restrict the search on a predefined outcome measure. This will enable us to locate as many studies on treatment of schizotypal disorder as possible. It will focus solely on studies including patients fulfilling the ICD and DSM diagnostic criteria for schizotypal disorder or STPD, respectively. The inclusion of studies addressing both the ICD and DSM diagnostic categories will provide a broader overview of treatment options for schizotypal disorder as a trait-like disorder, along with enabling the possibility of evaluating treatment effect based on studies using both diagnostic manuals. This combined approach will increase the statistical strength of the findings.

Possible limitations of this systematic review are the potential limited existing research on the topic as well as possible variations in methodology, interventions and outcome measures between included studies, which might affect the possibility to perform the planned meta-analysis. This might also affect the quality of recommendations or the possibility to make recommendations for clinical practice. Also, studies including patients with comorbid conditions will not be excluded in this review which might impact the findings on efficacy of tested interventions. We are, however, extracting data on comorbid conditions with the aim of using this information in the risk of bias assessment and in the GRADE evaluation in order to obtain a more nuanced assessment of the evidence.

We hope this review will provide inspirational guidance for research towards areas with missing evidence regarding treatment of schizotypal disorder.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

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