Psychosocial interventions for negative symptoms within schizophrenia, a systematic review

Protocol

Authors
Sjoerd J Vogel\textsuperscript{1,2}, Henderikus Knegethering\textsuperscript{1,2}, Mark van der Gaag\textsuperscript{2,3}, Stynke Castelein\textsuperscript{1,2}

Affiliation:
1. Lentis Center for Mental Health, Groningen, the Netherlands
2. Rob Giel Research Center, University Medical Center Groningen, Groningen, The Netherlands
2. Parnassia BAVO Institute, Den Haag, The Netherlands
3. V University, Amsterdam, The Netherlands

Contact information first author:
Sjoerd Vogel
University Medical Center Groningen
University Center for Psychiatry
P.O. Box 30.001
9700 RB Groningen
j.s.vogel@umcg.nl

This protocol is registered at Prospero (http://www.crd.york.ac.uk/Prospero/index.asp). Prospero is an international prospective register for protocols of systematic reviews, an initiative of the Centre for Reviews and Dissemination (UK).
Background

Description of the condition

Schizophrenia is considered one of the most debilitating mental health disorders. The syndrome is comprised by positive symptoms (psychosis), negative symptoms and cognitive disturbances [1]. The prevalence is estimated at 2.4 to 6.7 per 1,000 in developed countries, and at 1.4 to 6.8 per 1,000 in developing countries [2] and ranks 26 in the top 30 causes of the highest DALY’s (disability adjusted life years). DALY is a measurement for disease burden expressed in years lost due to illness or early death [3].

In the previous decennia, negative symptoms began to gain more attention by clinicians as it became apparent that they contribute a great deal of the disease burden in schizophrenia. Sadock et al. [2] wrote that the severity of negative symptoms best predict the long term disability. In a review, Mäkinen [4] states that negative symptoms are present in 50 - 90% in first episode psychosis [5-7].

Negative symptoms is a broad concept and "represent a loss or diminution of normal functions" [2]. The concept comprises five domains: blunted affect, alogia, asociality, anhedonia and avolition [8]. Sadock et al. [2] describes these as following: Blunted affect consists of an inability to understand or recognize displays of emotion from others; alogia is ‘a decrease in verbal communication’; avolition is defined as the loss of will or drive, closely related to anhedonia; anhedonia is a ‘loss of ability to find or derive pleasure from activities or relationships and an inability to express emotions; asociality includes ‘indifference to social relationships and decreases in the drive to socialize’.

As proposed by Carpenter [9], a distinction can be made between primary and secondary symptoms. Primary negative symptoms, also known as the deficit syndrome, are those symptoms that stem directly from the schizophrenia syndrome. Of all patients, 10-30% suffer from primary negative symptoms [2]. Secondary symptoms are related to treatment with antipsychotics and secondary effects of psychosis. For example, positive symptoms are a known cause of secondary negative symptoms in cases where patients try to protect themselves from paranoid experiences through social withdrawal. Another major cause of secondary symptoms is depression.

Following Carpenter, Kirkpatrick [10] proposed a separate disease for patients with primary persistent negative symptoms, known as the deficit syndrome. This separate disease hypothesis is confirmed by evidence [11]. Furthermore, a 20-year multi-follow-up longitudinal study provides evidence that patients with deficit syndrome have a persistently impaired course of illness and have poorer long-term outcomes compared to non-deficit patients [12].

Description of the intervention

Treatment of schizophrenia in recent history consists of drug treatment. It started with the founding of chlorpromazine in 1950, a so called first generation antipsychotic. First generation antipsychotics are known to cause harmful side-effects. Since the 1990’s a new generation of antipsychotics became available with less severe side effects. Nowadays, second generation antipsychotics are the first choice of treatment. A last resort treatment is electro convolution therapy (ECT). Both, antipsychotics and ECT are mainly effective in treating positive symptoms.
Parallel with the deinstitutionalization in mental health, psychosocial interventions became available. During the past decennia psychosocial interventions gained a much larger role in the treatment of schizophrenia additional to the treatment with antipsychotics. This is emphasized in several national guidelines. In 2012, the Dutch guideline for schizophrenia advised Cognitive Behavioural Therapy (CBT) to play a role in treatment. Summary’s of evidence show that, compared to other psychosocial interventions, most evidence is found for CBT [13]. The use of antipsychotics and psychosocial interventions greatly contributed to the treatment of positive symptoms in schizophrenia. However, there is not much evidence that suggests the effectiveness of these interventions on negative symptoms. In addition, no systematic review has been carried out to investigate the effects of psychosocial interventions on negative symptoms.

This systematic review aims to investigate all therapies for negative symptoms with the exception of drug therapy, invasive therapy, transcranial magnetic stimulation or therapy aiming at organic changes otherwise. With the exception of these therapies, this review will investigate psychosocial therapies and affiliated therapies, eg. running therapy, drama therapy, yoga or dance therapy.

**How the intervention might work**

The rationale for psychosocial interventions in schizophrenia is founded in the stress-vulnerability model [14]. The NICE guideline [15] underpins this theoretical foundation as follows: “In the stress-vulnerability model, individuals develop vulnerability to psychosis attributable to biological, psychological and/or social factors. Treatments, whether pharmacological or psychological, aim to protect a vulnerable individual and reduce the likelihood of relapse, reduce the severity of the psychotic episode and treat the problems associated with persisting symptoms. Psychological interventions may, in addition, aim to improve specific psychological or social aspects of functioning and may have a long-term effect upon an individual’s vulnerability”.

**Why it is important to do this review**

Negative symptoms are important in predicting poor social outcome [16] and long term disability, even better than psychosis [2]. Narvaez et al. [17] stress the importance of negative and depressive symptoms in the context of quality of life (QoL) and as treatment goals in schizophrenia. Other research also suggests an important role for negative symptoms in QoL [18-20].

Despite the growing attention for negative symptoms no adequate treatment options are available. A systematic review by Jiawan [21] found little evidence for the pharmacological treatment of negative symptoms. In addition, a meta-analysis by Leucht [22] showed also small effect sizes in favour of treatment with antipsychotics compared to placebo. However, decrease in negative symptoms rates are mainly due to treatment effects of secondary symptoms like depression. Despite treatment with antipsychotics, 35-70% of the patients remain suffering from negative symptoms [4]. No evidence is found to support any pharmacological interventions for the treatment of primary or persistent negative symptoms [11, 23]. Transcranial Magnetic stimulation is a relatively new treatment which is promising for the treatment of severe negative symptoms, although more research is needed [1].
Until now, no systematic review has been carried out in the broad spectrum of psychosocial interventions which are available in the treatment of negative symptoms. This review will comprehensively investigate the use of psychosocial interventions for negative symptoms. We will investigate all types of psychosocial interventions leading to recommendations on their effectiveness on negative symptoms.

**Objectives**

To investigate the effectiveness of psychosocial interventions for negative symptoms in patients with schizophrenia.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials measuring the outcome of psychosocial interventions on negative symptoms will be included. Cross-over designs will be excluded. Taking the interventions under research into account, the cross-over design has the potency of a carry-over effect which likely will cause bias in the estimate. Furthermore, only true randomized trials will be included in the review, because quasi randomized studies are prone to bias. Cluster randomised trials will be included provided that they have been scrutinized as they are prone to a unit of analysis error. As most studies include patients co-treated with antipsychotics, we will not exclude those studies.

**Types of participants**

Studies with patients from the age of 18 years and older with all types of schizophrenia as defined by the DSM-IV or ICD, are included in this review. Per study, the majority of included patients should have been diagnosed with schizophrenia. No limitations are held on sex or ethnicity. In addition, patients of all settings as well as all clinical stages will be included in the review. Studies concerning primary as well as secondary negative symptoms are eligible for inclusion. One could argue that secondary negative symptoms have a different pathophysiology and therefore should be analysed separately. Most studies however, don’t make any distinction between primary and secondary symptoms. Consequently, a systematic review would comprise too few studies in order to make an contribution to the base of knowledge. Furthermore, including both primary and secondary symptoms is considered appropriate [8].

**Types of interventions**

All therapies targeting negative symptoms will be included, with the exclusion of therapies aimed at operating through organic changes, eg drug therapy, transcranial magnetic stimulation or herbal therapies. Drug treatment as co-treatment will not be excluded. This review will include all psychotherapies and affiliated therapies, eg. running therapy, drama therapy, yoga or dance therapy. All comparisons and inactive control interventions are eligible for inclusion. No restrictions will be held on duration and intensity of therapy, nor the training of the therapist.
Types of outcome measures
Outcomes are grouped into short term (up to 12 weeks), medium term (13-26 weeks) and long term (over 26 weeks).

Primary outcome
1. Negative symptoms as assessed with the Positive And Negative Syndrome Scale (PANSS), Scale for Assessment of Negative Symptoms (SANS) or Brief Psychiatric Rating Scale (BPRS)

Search methods for identification of studies
Language is restricted to English and Dutch. We will document which studies are eligible studies in other languages, for the reader, to give insight in the available research.

Electronic searches
We will perform a search in CENTRAL, MEDLINE, EMBASE, CINAHL and PsychInfo. Search terms are included in appendix I.

Searching other resources
No other resources will be searched.

Data collection and analysis
Selection of studies
Selection of studies will be done by two reviewers: S. Vogel, registered nurse and student clinical epidemiology, and S. Castelein, Ph.D., medical sociologist. One reviewer (SV) will perform the electronic search in conjunction with a librarian. Possible eligible articles will be selected on the basis of title and abstract independently by SV and SC. Full text articles will be retrieved from selected articles and these will be independently scrutinized for eligibility by SV and SC. Multiple reports of the same study will be linked together. In case of any disagreement, a third reviewer (HK) will be consulted to reach consensus. If necessary, contact will be sought with authors to further clarify eligibility. A kappa static will be used to measure agreement. A flow diagram will be included to present the original number of studies and the subsequent exclusions of studies. A list of excluded studies that appear eligible will be included as an appendix.

Data extraction and management
Data will be extracted by one reviewer (SV) by the use of the Cochrane data extraction form, edited for this review. The items will be determined by two reviewers (SV and SC) and piloted in three studies. In addition, all data prone to subjective interpretation will be extracted by two reviewers (SV and SC). We will use coding and we will process the data using Microsoft Excel.
Assessment of risk of bias in included studies

Risk of bias will be assessed using Clinical Trials Assessment Measure – modified for psychological treatments (CTAM v4) [24]. The risk of bias will be assessed by two reviewers (SV and SC). In case of disagreement, a third reviewer (HK) will be consulted.

Measures of treatment effect

Dichotomous data

If possible, we will use Relative Risk (RR) as the effect measure for dichotomous data as this effect measure is the rather more intuitive to interpret data in contrast with Odds Ratio (OR).

Continuous data

Continuous data is preferably used over dichotomous data. Preferably, the change from baseline measures will be used.

Unit of analysis issues

Dealing with missing data

We will describe and assess studies with missing data. The potential impact of missing data on the findings will be discussed.

Assessment of reporting biases

Publication bias and reporting are known bias, leading to overoptimistic effects, because the majority of published studies tend to show significant results [25]. Reporting bias will be assessed by the use of a funnel plot. However, Niemeyer [26] found only moderate evidence for the presence of publication bias in meta-analysis about psychosocial interventions for schizophrenia.

Data synthesis

The aim of the analysis is to identify the treatment effect of all interventions, taking into account the appraisal of the underlying evidence. We will provide the evidence per intervention in a table, together with a narrative summary and discussion of the study’s findings according to the following structure: 1) What is the direction of the effect? 2) What is the size of the effect? 3) Is the effect consistent across studies? 4) What is the strength of evidence for the effect [25]?
References


APPENDIX 1 Search strategy

Medline, Embase, PsychInfo and Cochrane Register of Controlled Trials (OVID interface)

1. exp schizophrenia/ or exp psychosis/
2. (paranoid schizophrenia or paranoid psychosis).sh,id.
3. (schizo$ or hebephreni$).mp.
4. (training* or therap* or support* or treat* or technique* or intervention* or approach* or session* or program* or educat* or psychoeducat*).mp.
5. exp Rehabilitation/ or psychosocial rehabilitation.mp. or rehabilitation.mp. or exp Rehabilitation Nursing/ or exp Rehabilitation Centers/ or exp Rehabilitation Vocational/ or "activities of daily living"/ or animal assisted therapy/ or art therapy/ or dance therapy/ or exercise therapy/ or movement therapy/ or running therapy/ or music therapy/ or occupational therapy/ or recreation therapy/ or "rehabilitation of speech and language disorders"/ or rehabilitation, vocational/ or remission induction/ or cognitive therapy/ or CBT.mp. or cognit*.mp. or relaxation therapy/ or meditation/ or color therapy/ or crisis intervention/ or dance therapy/ or socioenvironmental therapy/ or schizophrenic psychology/ or "phenomena and processes (non mesh)"/ or "health care (non mesh)"/ or mindful*.mp. or exp Mind-Body Therapies/ or cognitive rehabilitation/ or rehabilitation counseling/ or occupational therapy/ or exp Group Psychotherapy/ or exp psychodrama/ or adventure therapy/ or exp Rehabilitation Vocational/ or "activities of daily living"/ or animal assisted therapy/ or educational therapy/ or self expression/ or bibliotherapy/ or exp exercise/ or running/ or exp Creative Arts Therapy/ or vocational education/ or adaptive behavior/ or disability management/ or exp behavior therapy/ or mindfulness/ or exp Awareness/ or exp cognitive behavior therapy/ or exp psychotherapeutic techniques/ or exp behavior modification/ or phototherapy/ or exp Cognitive Techniques/ or exp intervention/ or exp Milieu Therapy/ or psychosocial.mp. or adherence.tw. or exp psychotherapy/ or art*.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, dv, nm, kf, ps, rs, an, ui, tc, id, tm]
6. (non-drug* or non-pharmacol* or non-antipsychotic* or non-herb*).mp.
7. antipsychotic agents/ or drug therapy/ or pharmacokinetic$.mp.
8. (Amisulpride or Aripiprazole or Asenapine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Sertindole or Ziprasidone or Zotepine or halldol or haloperidol or lithium or amitriptyline or (Ketamine or Propofol) or (antidepressant$ or clomipramine or flufenazine or lithiumcarbonaat or citaloprine or venlafaxine or fluoxetine or zuclopentixol or fluoxetine or imipramine or lamotrigine or mirtazapine or paroxetine or sertraline) or (fluphenzine or Naloxone or Donepezil or Galantamine or Clonidine or Methylphenidate or dexamphetamine or dextroamphetamine or levamfetamine or nifedipine or vitamine D or d-serine)).mp.
9. (TMS or transcranial magnetic stimulation).mp.
10. ("ect" or electric shock therapy).mp.
11. (tobacco or smoking cessation or nicotin$ or cigarettes).mp.
12. (clinical trial$ or controlled clinical trial$).pt.
13. exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/
14. exp randomized controlled trials/ or exp randomized controlled trial/ or randomized controlled trials as topic/
15. (placebo$ or random$).ab.
16. (clinical trial$ or random$).pt.
17. animals/ not (animals/ and human$).mp.
18. (animal/ or animals/) not ((animal/ and human/) or (animals/ and humans/))
19. (animal not (animal and human)).po.
20. (systematic review or meta-analysis or cochrane).mp.
21. 1 or 2 or 3
22. 5 or 6
23. 7 or 8 or 9 or 10 or 11
24. 12 or 13 or 14 or 15 or 16
25. 17 or 18 or 19 or 20
26. 24 not 25
27. 22 not 23
28. 4 and 21 and 26 and 27

CINAHL (EBSCOhost interface)  Medline reference excluded

1. (MH "Schizophrenia+") OR "schizophr*" OR "schizofr*" or psychosis
2. training* or therap* or support* or treat* or technique* or intervention* or approach* or session* or program* or educat* or psychoeducat
3. (MH "Clinical Trials+") or (PT Clinical trial) or (TX clinic* n1 trial* or TX (singl* n1 blind*) or (singl* n1 mask*) or TX (doubl* n1 blind*) or (doubl* n1 mask*) or TX (tripl* n1 blind*) or (tripl* n1 mask*) or TX (trebl* n1 blind*) or (trebl* n1 mask*)) or (TX randomi* control* trial*) or (MH "Random Assignment") or (TX random* allocat*) or (TX placebo*) or (MH "Placebos") or (MH "Quantitative Studies") or (PT Randomized controlled trial)
4. tobacco or smok* cessation or nicotin$ or cigarette*
5. pharmaco$ or (drug therapy) or (MH "Antipsychotic Agents+")
6. TMS or transcranial magnetic stimulation
7. (MH "Animals+")
8. (MH "Genes, BRCA") OR (MH "Genes+") or gene*
9. (Amisulpride or Aripiprazole or Asenapine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Sertindole or Ziprasidone or Zotepine or haldol or haloperidol or lithium or amitriptyline) or (TMS or transcranial magnetic stimulation) or (ect or electric shock therapy) or (Ketamine or Propofol) or (antidepressant* or clomipramine or flufenazine or lithiumcarbonaat or citalopram or duloxetine or venlafaxine or flupentixol or zuclopenthixol or fluoxetine or imipramine or lamotrigine or mirtazapine or paroxetine or sertraline) or (fluphenazine or Naloxone or Donepezil or Galantamine or Clonidine or Methylphenidate or dexamphetamine or dextroamphetamine or levamfetamine or nifedipine or (vitamine D) or d-serine)
10. (MH "Cochrane Library") OR (MH "Systematic Review") OR (MH "Meta Analysis") or review* or systematic or meta$ or PT case report or (MH "Qualitative Studies+") OR (MH "Field Studies") or phenomenological research or narratives or commentary or conference
11. 1 and 2 and 3
12. 4 or 5 or 6 or 7 or 8 or 9 or 10
13. 11 not 12