Psychosocial Interventions for People with Schizophrenia or Psychosis on Minimal or No Antipsychotic Medication: A Systematic Review

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Abstract

Antipsychotics are the first-line treatment for people with schizophrenia or psychosis. There is evidence that they can reduce the symptoms of psychosis and risk of relapse. However many people do not respond to these drugs, or experience adverse effects and stop taking them. In the UK, clinical guidelines have stressed the need for research into psychosocial interventions without antipsychotics. This systematic review examines the effects of psychosocial interventions for people with schizophrenia or psychosis who are on no/minimal antipsychotics. Databases were searched for empirical studies investigating a psychosocial intervention in people with a schizophrenia spectrum disorder who were not taking antipsychotics or had received an antipsychotic minimisation strategy. We identified nine interventions tested in 17 studies (N=2,250), including eight randomised controlled trials. Outcomes were generally equal to or in a small number of cases better than the control group (antipsychotics/treatment as usual) for Cognitive Behavioural Therapy (CBT), Need Adapted Treatment and Soteria. The remaining interventions provided some encouraging, but overall inconsistent findings and were Psychosocial Outpatient Treatment, Open Dialogue, Psychosocial Inpatient Treatment, Psychoanalysis/Psychodynamic Psychotherapy, Major Role Therapy, and Milieu Treatment. Study quality was generally low with little recent research. In conclusion, nine psychosocial interventions have been studied for patients on no/minimal antipsychotics, The majority of studies reported outcomes for the intervention which were the same as the control group, however, study quality was problematic. Given the adverse effects of antipsychotics and that many people do not want to take them, high quality trials of psychosocial treatments for people on minimal/no antipsychotics are needed.

Key words: schizophrenia; psychological treatments; not taking antipsychotics; minimal antipsychotics; alternative treatments.

1. Introduction

Since their introduction in the 1950s, antipsychotics have become the first line treatment for people with schizophrenia or psychosis. There is evidence that they can reduce the symptoms of acute psychosis, and risk of relapse (Leff and Wing, 1971; Leucht et al., 2013, 2012). However, up to a third of patients do not respond to these drugs (Lindenmayer, 2000) and recent concerns have been raised about their long-term use (Moncrieff, 2015; Murray et al., 2016). Concerns include the common experience of adverse effects such as weight-gain, cardiovascular and metabolic problems (De Hert et al., 2011; Rummel-Kluge and Komossa, 2010), and sexual dysfunction (Knegtering et al., 2003; Laxhman et al., 2017). As a result, in routine practice up to 40-74% of people stop taking antipsychotics (Lacro et al., 2002; Lieberman et al., 2005).

Psychosocial treatments, such as family therapy and cognitive behavioural therapy (CBT), are also recommended for schizophrenia and psychosis as adjunctive to antipsychotics, and have been found to be beneficial (Gottdiener and Haslam, 2002; Lehman et al., 2010; NICE, 2014; Read and Ross, 2003). Given the growing concerns about long-term antipsychotic prescription and that many people stop taking these drugs, in the UK the National Institute for Health and Care Excellence (NICE) Schizophrenia Guideline has emphasised the need for increased research into the effectiveness of psychosocial interventions without antipsychotics (Carrà et al., 2007; NICE, 2014).

The majority of research into psychosocial interventions for psychosis or schizophrenia without or with an antipsychotic minimisation strategy (which aims to reduce the use of antipsychotics, such as through postponing antipsychotic prescription) was conducted in the 1960s-90s. These included the therapeutic community, Soteria House (Bola and Mosher, 2003; Mosher et al., 1975), psychoanalytic or psychodynamic psychotherapy (May et al., 1981), and the family and social network approach to care, Need Adapted Treatment, subsequently developed as Open Dialogue (Seikkula et al., 2003). A small number of systematic reviews of these interventions

have been conducted (Bola et al., 2009; Calton et al., 2008; Malmberg et al., 2001). A review of Need Adapted Treatment concluded improvements to be in favour of this intervention with a small effect size (Bola et al., 2009). A review of Open Dialogue concluded initial findings to be promising but low study quality meant conclusions could not be drawn about efficacy (Freeman et al., 2018). A review of the Soteria approach concluded it to have equal and in certain areas better outcomes than those treated with antipsychotics as usual (Calton et al., 2008). A meta-analysis (Malmberg et al., 2001) and systematic review (Mueser and Berenbaum, 1990) of psychodynamic psychotherapy, which included studies in unmedicated patients, concluded this to be inferior to treatment with antipsychotics.

There has yet to be a systematic review which summarises all such interventions. Given this, and the need for more research into no or minimal antipsychotic treatments, we conducted a systematic review which aimed to summarise the main effects (for relapse, symptoms, and function) for all studies of psychosocial interventions for people with psychosis or schizophrenia who were not taking antipsychotics or received an antipsychotic minimisation strategy.

2. Methods

We conducted a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines (Moher, Liberati, Tetzlaff, 2009). The review protocol is registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016045787).

2.1 Eligibility criteria

Studies were included if they were an empirical study that examined a psychosocial intervention in people with a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, delusional disorder, non-affective psychosis, psychotic disorder) who were either not

taking antipsychotics (including placebo), or were receiving an antipsychotic minimisation strategy (such as intermittent treatment, where antipsychotics are taken only when the person is symptomatic or antipsychotic postponement, where antipsychotics may not be prescribed for the first 2-6 weeks). Given the anticipated heterogeneity of studies and that we aimed to include all studied interventions to date, there was not the requirement for a control group. There were no restrictions on participant age or date. Studies not published in the Latin based alphabet were excluded.

2.2 Search strategy

The following databases were searched from inception to March 2019: Ovid MEDLINE, EMBASE, PsycINFO, Psycarticles, Open Grey, Scopus, AMED, The Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and The Cumulative Index to Nursing and Allied Health Literature (CINAHL). Unpublished or ongoing studies were searched for on ClinicalTrials.gov and the ISRCTN registry for clinical trials. Search terms are listed in Text S1 (Supplement).

2.3 Data selection, extraction, and outcomes

Titles and abstracts were screened by RC and NL, full text eligibility was assessed by RC, NL, and SP, data extraction was conducted by RC and NL.

2.4 Quality assessment

Quality ratings for randomised studies was assessed with the Cochrane Handbook Risk of Bias Tool (Higgins and Green, 2011). Each study was rated as high, low, or unclear risk of bias in 6 domains: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective reporting. For non-randomised studies we used the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool (Thomas et al., 2004). Each study was rated as strong,

moderate or weak for 6 domains: selection bias, study design, confounders, blinding, data collection methods, withdrawals and drop-outs. Intervention integrity, appropriate analysis, and selective reporting were also rated for these studies. The Cochrane tool is widely used and the EPHPP has been judged to be suitable for use in systematic reviews of effectiveness (Deeks et al., 2003). Before commencing independent quality assessment, reviewers (NL, NC, and RC) assessed the same 5 papers, with high interrater reliability (96%). The remaining papers were then independently assessed, with regular meetings to discuss queries. SP and RC then met to review all ratings and reach a consensus on quality scoring.

2.5 Analysis

Qualitative synthesis: Study and intervention characteristics and results were summarised by RC and checked by NL. Greater emphasis was placed on RCTs or controlled cohort studies. Where possible, authors or colleagues trained in the intervention were asked to confirm that they agreed with our identification of the main characteristics of the given intervention with amendments made as advised.

Quantitative synthesis: We aimed to summarise effects for relapse, symptoms, and function (e.g. social, occupational) as these were the three main outcomes measured across the included studies. For relapse, we reported number re-hospitalised, symptomatic relapse, or the most proximal measure, we also reported length of hospital stay for inpatient studies. For symptoms, we preferentially reported the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), or the most proximal measure. For function, unless a primary measure was specified, all measures for which there were available data were reported. Where multiple control groups were reported, we compared to the antipsychotics as usual control or standard care.

Where appropriate effect sizes (e.g. Cohens *d*, Mean Difference) were not reported and where the necessary data were provided we calculated effect sizes. For continuous data we

preferentially calculated Cohen's *d* using the mean pre-to post-treatment change, minus the mean pre-to post-placebo group change, divided by the pooled pre-test standard deviation (SD) with a bias adjustment (Cohen's *d* classed as; 0.2=small, 0.5=moderate, 0.8=large) (Cooper et al., 2015a, 2015b; Morris, 2007). Where only endpoint scores were provided we calculated the Mean Difference using the inverse variance method with fixed effects in RevMan 5.3 ("Review Manager (RevMan) [Computer program] Version 5.3.," 2014). For dichotomous data we calculated the risk ratio (RR) using the Mantel-Haenszel method with fixed effects in RevMan 5.3. Where appropriate data were not provided we reported the results (e.g. *p*-values) provided in the paper. The heterogeneity of study design and low quality of data reporting meant a meta-analysis was not feasible.

3. Results

3.1 Study selection

The search strategy identified 6,361 references. Of these, 264 full text articles were assessed for eligibility with 237 excluded (see Figure 1 for reasons for exclusion) and 17 studies, published in 27 papers, with a total of 2,250 participants included.

Insert Figure 1 here

3.2 Study characteristics

Study characteristics, including antipsychotic strategy, study quality and detailed intervention descriptions are in Table 1 and Table S3 (Supplement). Of the 17 studies, 15 were controlled studies: 8 randomised controlled trials, 1 quasi-experimental cohort study, 4 controlled cohort studies, 1 controlled trial (with unclear allocation method), 1 observational study which included a comparison group, and 2 were uncontrolled studies: 1 exploratory trial, 1 cohort study. Participants either had chronic conditions (N=1), were first episode/early intervention (N=7), or both (N=9).

Insert Table 1 here

3.3 Quality of included studies

Quality scores are summarised in Table 2 and in detail in Tables S1 and S2. For the 9 non-randomised studies, concerns were lack of blinding (7=weak) and potential confounders (4=weak). Data collection tools were relatively good (6=strong, 3=weak). Selection bias, study design, and withdrawals and dropouts were mainly rated as moderate quality. One study showed evidence of selective reporting. Seven studies did not report whether participants may have received an unintended intervention and 4 studies did not use appropriate statistical analysis.

For the 8 randomised studies, the main concerns were a lack of blinding of patients and people delivering the interventions (5 high risk, 3 unclear risk) and incomplete outcome data (4 high risk, 2 unclear risk, 2 low risk). Random sequence generation (4 low risk, 4 unclear risk) and blinding of outcome assessors (4 low risk, 2 unclear risk, 2 high risk) were less of a concern. Allocation concealment was generally unclear risk and there was little evidence of selective reporting. Other main concerns were small sample sizes in 5 studies and issues with data reporting and analysis in 4 studies.

Insert Table 2 here

3.4 Interventions

Nine psychosocial interventions for people with schizophrenia or psychosis on no or minimal antipsychotics have been studied: Need Adapted Treatment, Open Dialogue, Psychoanalysis/Psychodynamic Psychotherapy, Major Role Therapy, Soteria, Psychosocial Outpatient and Inpatient Treatment, Milieu (inpatient) Treatment, and CBT. Interventions included established methods, such as psychoanalysis and CBT, and less standardised psychosocial approaches. Few studies described how the treatment delivered was standardised

and how quality of implementation was assured. The trials of CBT used regular supervision, rated recordings of sessions with a cognitive therapy scale (Blackburn et al., 2001), and reviewed written, structured session records (Morrison et al., 2018, 2014). Results are grouped by intervention, including a brief general summary of each intervention. For a detailed description of each intervention and control group by study see Table S3 (Supplement). Table 3 reports treatment effects for relapse or length of hospital stay, symptoms, and function for controlled studies.

Insert Table 3 here

Table 4 compares the central characteristics of each intervention. Across all interventions the only consistent characteristic was that they included individual sessions. The interventions used a wide range of strategies, most commonly including: group sessions, social network involvement or aiming to develop social networks, they lasted over a year, provided practical support such as managing finances, employed a multimodal approach by involving a number of different therapeutic approaches, and focused on external factors such as employment support.

Insert Table 4 here

3.4.1 Cognitive Behavioural Therapy (CBT)

2 RCTs (Morrison et al., 2018, 2014), 1 exploratory trial (Morrison et al., 2012).

CBT is a problem oriented, individual, short-term therapy. The CBT used in these trials was specifically developed for people with psychosis (see Morrison, 2017 for a detailed description). The main features include: normalising interpretations of events (e.g. discussion of the high prevalence of psychotic experiences in non-clinical populations), examining the advantages/disadvantages of events, interpretations and responses (e.g. considering the advantages/disadvantages of paranoid or suspicious thoughts or resisting or engaging with voices), understanding the potential causes of these events or interpretations, helping people to

test their interpretations through behavioural experiments, consider alternative explanations, and develop coping strategies. One of the aims is to reduce stress, fear, and catastrophizing and improve quality of life (Table S3).

Antipsychotic strategy: Unmedicated with antipsychotics.

Results: Two single blind RCTs have been conducted (Morrison et al., 2018, 2014). The first RCT found that CBT compared to an antipsychotic-free treatment as usual control group, significantly reduced the primary outcome, symptoms of psychosis at moderate effect (*d*=0.5, *p*=0.003), and improved social function (Est=5.47, *p*=0.04) (Morrison et al., 2014). One more person in the intervention than control (5 vs. 4) were hospitalised during the study and 2 people in each group experienced a symptomatic deterioration (Table 3). During the study, in both groups 10/37 people were prescribed antipsychotics. The second RCT compared CBT to an antipsychotic only control group (Morrison et al., 2018). No differences between the groups were found for symptoms of psychosis or social function. Two people vs. 0 people in the CBT vs. control group were hospitalised during the study (Table 2). During the study 8/26 people in the CBT group received antipsychotics and 8/24 people in the antipsychotic group did not receive antipsychotics.

An exploratory uncontrolled trial found 9 months of CBT to significantly improve symptoms of schizophrenia with a large effect size (*d*=0.9-1.3), significant moderate to large improvements were also found for recovery (*d*=0.7) and social functioning (*d*=0.5-0.9) (Morrison et al., 2012).

Harms: In Morrison et al (2014) 8 serious adverse events were reported, 2 in the CBT group and 6 in the control group and 2 participants in each group were judged to have a deterioration. In Morrison et al (2018) adverse side-effects (e.g. sleep or memory problems) were less common in the CBT group than the antipsychotics group (p=.017). One participant in the CBT group and 2 in the antipsychotics group were judged to have deteriorated during the study. One serious

adverse event was thought to be related to the study, an overdose of 3 paracetamol tablets in the CBT group. In Morrison et al (2012) 2/20 participants deteriorated during the study.

3.4.2 Psychosocial outpatient treatment

2 RCTs (Carpenter et al., 1990, 1987).

Psychosocial outpatient treatment had three main components: 1) weekly meetings with a therapist or case manager; 2) psychoeducationin family/carer meetings: to learn about schizophrenia and psychosis, discuss potential stressors which may have led to the development of these conditions, methods to reduce these stressors, signs of relapse, crisis management, and to establish relationships between families/carers and the clinical team; 3) increasing social activities (Table S3) (Carpenter and Heinrichs, 1983).

Antipsychotic strategy: Intermittent treatment with antipsychotics.

Results: Both RCTs were conducted by William Carpenter and colleagues. The first trial compared the intermittently medicated intervention group to a group continuously medicated with antipsychotics (Carpenter et al., 1987). At two years slightly more people were hospitalised in the intermittently medicated group (11 vs. 9, RR=1.16, 95% CI 0.62-2.19), but there were no differences in symptoms or function. In the second trial, both the intermittently medicated and continuously medicated group received the psychosocial intervention (Carpenter et al., 1990). At 2 years more people in the intermittently medicated group were hospitalised (30 vs. 21, RR=1.48, 95% CI 0.97-2.26) or had experienced a deterioration (M(SD)=4.21(3.70) vs. 2.75(2.56), MD=1.46, 95% CI 0.30-2.62) in the continuously medicated group. The continuously medicated group also had better functioning ($p<.01$), driven by better employment rates, no difference was found for symptoms (Table 3). In both studies, the intermittently medicated group took antipsychotics for less time (e.g. 52% vs 90% (Carpenter

et al., 1990)) and were on a lower dose than the continuously medicated group (e.g. 196mg vs. 720mg chlorpromazine equivalents, p<.05 (Carpenter et al., 1987)).

Harms: Harms other than relapse rates and deterioration are not reported.

3.4.3 Psychoanalysis and psychodynamic psychotherapy

3 RCTs (Karon and Vandenbos, 1972; May et al., 1981, 1976), 1 controlled trial (unclear allocation method) (Gottlieb et al., 1951)

In psychoanalysis/psychodynamic psychotherapy, the therapist aims to elicit people's past emotional experiences, helping them to understand and change their role in influencing their current inner world and behaviour (Table S3).

Antipsychotic strategy: Unmedicated with antipsychotics, one study medicated with a placebo (Grinspoon et al., 1968).

Results: One of the largest and most influential studies was an RCT conducted by Philip May and colleagues (May et al., 1981; May and Tuma, 1964) that compared psychodynamic psychotherapy to multiple control groups, including antipsychotics only. Follow-ups were conducted up to 5 years from discharge. Results showed that people who received antipsychotics alone spent less time in hospital than those who received psychotherapy only (395 days vs. 225 days, D<.01[1]). Once discharged, there was no significant difference in the number of days rehospitalised. For the total sample at 2 years following discharge, those who received antipsychotics alone, compared with psychotherapy alone, spent longer working for pay (MD=-1.10, 95% CI=-1.78 to -0.42) and had lower levels of symptoms (MD= -5.8, 95% CI -9.99 to -1.6). The antipsychotic only group were reported to have better ratings of relationships and occupational and social adjustment (rated by social workers) although statistical tests are

[1] D=The significance given by a Duncan New Multiple Range Test, p-values were not provided in this paper.

not reported it states, 'the drug effect was generally not significant'. In another large study a 'brief' version of psychodynamic psychotherapy (average of 7 weeks of treatment (range=1-27 weeks)) was compared with electroconvulsive therapy (ECT). Over the four year follow-up period no differences were found between social recovery or a clinical judgement of improvement. In a small inpatient RCT conducted by Messier and colleagues (Messier et al., 1969) in comparison to the antipsychotic only control group, at 1 and 3 years, no differences were found for symptoms, or function. In another very small RCT (Karon and Vandenbos, 1972), at a 20-month follow-up, 3 inpatients receiving psychoanalysis with an experienced therapist, had shorter hospital stays (p<.05), fewer rehospitalisations (p<.05) and better function (p<.05) compared to antipsychotics only (Table 2). In May et al., (1981) treatment was not controlled after discharge, and those who received psychotherapy alone received antipsychotics less frequently (60%) than those who received antipsychotics alone (90-95%). The outcome for the antipsychotic status of participants in other studies is not clearly reported.

Harms: In May et al (1981) 2 people in the antipsychotic only and 1 in the intervention group committed suicide. Harms were not reported in the remaining studies.

3.4.4 General Inpatient Milieu

1 RCT (May et al., 1981, 1976).

The 'milieu' describes the general treatments and atmosphere of an inpatient ward. In this study this consisted of routine nursing care, sedation, hydrotherapy, occupational, and recreational therapies, ward meetings, and social case work (Table S3).

Antipsychotic strategy: Unmedicated with antipsychotics.

Results: The trial conducted by Philip May and colleagues (May et al., 1981; May and Tuma, 1964) included an antipsychotic-free 'milieu' group. They found that people who received

antipsychotics only spent less time in hospital than those who received milieu therapy (345 days vs. 225 days), although the statistical significance of this difference is not reported. Once discharged however, there was no significant difference in the number of days rehospitalised and in the whole sample at the 2 year follow-up there were no differences reported for symptoms, proportion of time working for pay, and relationships and occupational and social adjustment (rated by social workers) (Table 3). Treatment was not controlled after discharge, and those in the milieu group received antipsychotics less frequently (62%) than those who received antipsychotics alone (90-95%).

Harms: Two people in the antipsychotic only group committed suicide.

3.4.5 Major Role Therapy

1 RCT (Hogarty et al., 1974b, 1974a; Hogarty and Goldberg, 1973).

Major Role Therapy (MRT) consisted of intensive individual social casework and employment rehabilitation, with the aim being to resolve personal or environmental problems, and improve social relationships (Table S3).

Antipsychotic strategy: MRT + placebo.

Results: One RCT has been conducted, at a 3 year follow-up those receiving antipsychotics only had lower rates of relapse than those receiving MRT + placebo (53% vs. 78%). Analysis of this difference is not reported but antipsychotics were found to have a significant effect on reducing relapse (p<.001). Symptoms and function were unreported for the total sample (they were reported only for a sub-sample of people who had not relapsed) as was the adherence to the antipsychotic strategy.

Harms: 3 people had an allergic reaction to the antipsychotic, 1 person discontinued the antipsychotic because it interfered with their employment.

3.4.6 Soteria

1 controlled cohort study, 1 RCT (Soteria USA, 2 cohorts) (Bola and Mosher, 2003), 1 RCT (Soteria Berne, randomisation was constrained by bed availability) (Ciompi et al., 1993, 1992, 1991).

Intervention: The Soteria approach was a residential treatment programme which aimed to allow people to go through an episode of psychosis with high levels of support and minimal interference. Those experiencing an episode of psychosis received constant 1-1 support, with the aim to find meaning in the subjective experience of psychosis (Table S3).

Antipsychotic strategy: Antipsychotic postponement.

Results: For Soteria USA, results are reported at 2 years across both cohorts. Those in the intervention compared with the control group (antipsychotics as usual on an inpatient ward) had a higher chance of living alone or with peers (Est=0.18, $p<.05$), and there were no differences in rates of readmission, symptoms, social function, or employment[2]. In a subsample of 63 patients diagnosed with schizophrenia, those in the intervention compared to control had better and more improved global psychopathology (Est=.34, p<.05) and better social functioning (Est=.64, p<.05). For Soteria Berne (which used the Soteria model), at 2-years there were no significant differences between the intervention and control group (antipsychotics as usual on an inpatient ward) for relapse, symptoms, or function (Table 3). In both studies, residents in Soteria received significantly less antipsychotics than the control groups, e.g. in Soteria USA, at one-year, 10% of the intervention vs. 75-100% in the control group received antipsychotics (Mosher et al., 1975).

[2] We report results from the 'endpoint analysis' as this is closest to an 'intent to treat' analysis which we preferentially reported. A 'completers' analysis also reported the intervention compared to control group to have a significant reduction in symptoms (Est=0.21, $p<.05$).

Harms: Aside from relapse harms are not reported for Soteria USA. In Soteria Berne it states that there were three incidents where a patient incurred serious harm to themself or others.

3.4.7 Need Adapted Treatment

2 controlled cohort studies: The Acute Psychosis Integrated (API) Treatment Project (Lehtinen et al., 2000) and the Swedish Parachute Project (Cullberg et al., 2006, 2002).

Need Adapted Treatment, developed in Finland, consisted of an initial family centred intervention, individual psychotherapy, family therapy, group therapy, and home visits. Treatment was guided by a number of key principles (Table S3).

Antipsychotic strategy: Antipsychotic postponement.

Results: The Acute Psychosis Integrated (API) Treatment Project compared to a control group that used a modified form of Need Adapted Treatment with antipsychotics as usual (Lehtinen et al., 2000): at 2-years the intervention group had spent less time in hospital than the control (50.8% vs. 25.6% < 2 weeks in hospital, p=.01) and had better functioning (49.2% vs. 25% scored ≥ 7 Global Assessment Scale, p=.02). There were no differences in symptoms, employment, or another measure of function (the 'Grip on Life' assessment (Salokangas et al., 1989)). At 2-years, 42.9% in the intervention vs. 5.9% in the control had not received any antipsychotics (p<.001).

The Swedish Parachute Project used a historical control group which were treated with antipsychotics according to usual practice (Cullberg et al., 2006, 2002). The total sample was followed up after 1 year and a subsample of those with a diagnosis of schizophrenia were followed up at 3 years. At 1 and 3 years, the intervention group had better functioning measured using the Global Assessment Scale (Endicott et al., 1976) (1 year: p<.05, figures not provided, 3 years: d=0.97, 95% CI 0.93-1.01) and there were no differences in nights spent in inpatient care (Table 3). At 3 years, fewer people in the intervention than control group had

taken disability benefits or sick leave for >12months (38% vs. 59%, p<.05). At 1 and 3 years there were no differences between the control and intervention in the dosage or use of antipsychotics. At 3 years, all participants had been treated with antipsychotics at some point during the study although at the time of assessment levels of prescribing would be considered low in both groups (58% received antipsychotics in the intervention vs. 63% in the control).

Harms: Lehtinen et al (2000) do not report harms, Cullberg et al (2006) reported 1 person in the intervention and 2 in the control group committed suicide.

3.4.8 Open Dialogue

1 controlled cohort study (Seikkula et al., 2003), 1 cohort study (Seikkula et al., 2011).

Developed from Need Adapted Treatment, Open Dialogue is a psychosocial approach to treatment that involves a consistent family and social network approach to care, all staff receive training in family therapy and related psychological skills (Table S3).

Antipsychotic strategy: Antipsychotic postponement.

Results: The controlled cohort study compared an Open Dialogue group (N=23) to a historical control group (N=14) that used a modified form of Need Adapted Treatment with antipsychotics as usual. Results from this study should be interpreted with caution as the control group was small, from a different area of Lapland, and data for this group were collected 2 years earlier with no controlling for potential confounders (such as different practices for patient hospitalisation). As such effect sizes have not been calculated. At a 2 year follow-up fewer people in the intervention than control group had experienced a relapse (26% vs. 71%), the intervention group also had better levels of function, measured by the Global Assessment Scale (Int/Control baseline: M=2.8(SD 0.64)/4.2(0.89), FU: 5.7 (1.3)/4.9 (1.6)), were more likely to be working or studying (65% vs. 21% studying or working), and there was no difference in

symptoms measured with the BPRS (Table 2). At 2 years, fewer people in the open dialogue group were taking ongoing antipsychotics than in the control group (17% vs. 71%, $p<.05$).

The (non-controlled) cohort study was conducted in a separate sample of participants with first episode psychosis (N=18) who had received Open Dialogue at a later date. At two years 72% of participants had not experienced a relapse, only 12% were unemployed, and 28% were taking antipsychotics (Seikkula et al., 2011).

Harms: Not reported.

3.4.9 Psychosocial (inpatient) treatment

1 controlled observational study (Carpenter, 1977).

Psychosocial Inpatient Treatment involved psychoanalytic psychotherapy, group therapy, and family therapy. The inpatient ward environment was also described as a therapeutic milieu (Table S3) (Carpenter, 1977).

Antipsychotic strategy: Unmedicated with antipsychotics.

Results: At 1 year after admission for the intervention and 2 years for the control group, who had received antipsychotics as usual on an inpatient ward (data were collected independently without the initial intention of comparing the two cohorts), mean outcome scores (combined scores of function, time spent in hospital, symptoms) for the intervention were better than the control (12.7 vs.11.1, MD=1.6, 95% CI 0.32-2.88) (Table 3). For the duration of the study 27/49 people were unmedicated in the intervention. Figures were not provided for the control.

Harms: Not reported.

3.4.10 Summary of results from controlled studies

Table 5 reports that across the outcomes of relapse, symptoms and function, the majority of studies reported no difference between the intervention and control groups (N=21 outcomes), in a minority of cases outcomes were better than (N=7 outcomes) or poorer than (N=8 outcomes) the control group. In 3 studies multiple measures of function were taken with none identified as the primary measure and mixed results reported**.**

4. Discussion

This systematic review has found that nine psychosocial interventions have been studied for people with schizophrenia or psychosis who were unmedicated or taking minimal antipsychotics. For controlled studies, we report comparisons of relapse, symptoms, and function between the intervention and control (generally antipsychotics as usual[3]). Effect sizes were varying and given the methodological limitations of the studies with only 8 RCTs, and low quality scores in some domains, results require replication in high quality RCTs and should be interpreted with caution. The majority of studies reported outcomes for the intervention which were the same as the control group, a smaller number reported outcomes which were either better than or poorer than the control group. Outcomes were generally equal to or in some cases better than the control group for CBT (Morrison et al., 2018, 2014), Need Adapted Treatment (Cullberg et al., 2006; Lehtinen et al., 2000), and Soteria (Bola and Mosher, 2003; Ciompi et al., 1991). Results were more mixed for the remaining studies. Psychosocial Outpatient Treatment (Carpenter et al., 1990, 1987) had relatively similar outcomes when only the intermittent medication group received the psychosocial treatment. However, the continuously medicated group fared better when they also received the psychosocial treatment. For Psychoanalysis (Karon and Vandenbos, 1972; Messier, 1969) and Psychodynamic Psychotherapy (Gottlieb et al., 1951; May et al., 1981, 1976), there were more positive results from two smaller studies, and in one larger study a 'brief' version of psychotherapy was found

[3] Aside from: CBT which, in one study was compared with an unmedicated treatment as usual group, psychosocial outpatient treatment which, in a second study, compared to psychosocial outpatient treatment with antipsychotics and 'brief' psychodynamic psychotherapy which compared to ECT.

to have similar outcomes to those receiving ECT. However the largest study to compare to medication found generally better outcomes for the antipsychotic only group (May et al., 1981). For milieu therapy (May et al., 1981, 1976), aside from longer hospital stays there were no other differences between this treatment and the antipsychotic only group. In Major Role Therapy those taking placebo experienced a higher rate of relapse (Hogarty et al., 1974b, 1974a; Hogarty and Goldberg, 1973). Due to methodological issues, effect sizes were not reported for Open Dialogue (Seikkula et al., 2003) which reported generally positive results for the intervention. Psychosocial (inpatient) treatment (Carpenter, 1977) gave positive results for the intervention, however is supported only by a controlled observational study at present.

The interventions included a wide range of varying characteristics, including individual and group sessions, social network involvement and development, were both long and short term treatments, and focusing both on internal (e.g. managing emotions) and external (e.g. employment support) factors. This indicates that a wide range of varying strategies can be employed in such treatments.

Due to the small number of participants and low study quality, it is difficult to assess whether there was any evidence of greater harm for the minimal antipsychotic intervention groups and these results should be interpreted with caution. Five studies reported no difference in relapse rates, 4 studies reported more relapses in the intervention than control group and 2 studies reported fewer relapses in the intervention group. Only 4 studies reported other adverse events, in these studies there was no evidence of more harm for the no/minimal antipsychotic intervention.

Our results are in line with previous reviews (Bola et al., 2009; Calton et al., 2008; Freeman et al., 2018; Malmberg et al., 2001). Bola et al., (2009) reviewed the effectiveness of psychosocial treatments involving an antipsychotic postponement strategy, which included Soteria, and Need Adapted Treatment. In agreement with our interpretation of similar or in some cases better

outcomes, compared to the control groups, they concluded there to be a small treatment effect (*r*=0.1-0.2) favouring the intervention. A systematic review of the Soteria approach suggested this treatment to be at least as effective and in some cases better than treatment as usual in a hospital (Calton et al., 2008). A meta-analysis (Malmberg et al., 2001) and a systematic review (Mueser and Berenbaum, 1990) of psychodynamic psychotherapy, which include the May et al., (1981) study in unmedicated patients, concluded this intervention to generally have poorer outcomes than treatment with antipsychotics. A review of Open Dialogue concluded initial findings to be promising but low study quality meant conclusions could not be drawn about efficacy (Freeman et al., 2018).

Our results are also in line with evidence from randomised (Wunderink et al., 2013) and non-randomised studies (Harrow et al., 2014), which have shown that not all people with schizophrenia or psychosis may require continuous treatment with antipsychotics. A cohort study reported poorer outcomes for those on continuous antipsychotic treatment 15-20 years after first experiencing psychosis (Harrow et al., 2012). An RCT which compared antipsychotic reduction with maintenance treatment reported successful discontinuation of antipsychotics in 20% of people (Wunderink et al., 2007), and greater rates of social recovery in the reduction group at a 7-year follow-up (Wunderink et al., 2013). A more recent trial of antipsychotics found that during the trial 15.7% of people decided to stop all antipsychotic medication and of this group 76.5% did not experience a relapse during the study observation period (Landolt et al., 2016). However, the follow-up length in this study was relatively short (12 months) meaning that relapses could have occurred after the end of the study. The finding, that not all people may require continuous antipsychotic treatment, supports the need for further research into interventions for people who choose not to take these drugs or wish to take the minimal amount.

Although conversely, it is important to note research which has suggested potentially poorer outcomes for people who discontinue or never take antipsychotics. A 10-year follow up of a

randomised trial of antipsychotic discontinuation versus maintenance treatment found a poorer clinical outcome in the discontinuation compared to maintenance treatment group (39% had a poor clinical outcome vs. 21%) (Hui et al., 2018). A comparison between antipsychotic- treated and never-treated people with schizophrenia in China found lower levels of remission for those who had not received treatment (Ran et al., 2015).

4.1 Strengths and limitations

To our knowledge this is the first systematic review to summarise the characteristics and results of psychosocial interventions for people with schizophrenia or psychosis, who are not taking antipsychotics or receiving an antipsychotic minimisation strategy. Our broad inclusion criteria (any empirical study) and systematic search in a large number of databases meant that we identified a wide variety of interventions tested for people who were experiencing both chronic and acute psychosis. Our research team includes psychologists and psychiatrists who are able to provide different perspectives on the interpretation of results. Study authors or colleagues trained in these approaches were included when identifying the intervention characteristics, ensuring this analysis was accurate.

The poor quality of the majority of included studies limits our interpretation of results. Only 8/17 studies were RCTs and quality ratings highlighted significant concerns with lack of blinding, potential confounders, and incomplete outcome data. This may have led to bias (Deeks et al., 2003; Wood et al., 2008). Other limitations were as follows. Although the studies included a total of 2,250 people, this number is small in comparison to medication trials, with a recent meta-analysis of antipsychotic effectiveness including 43,049 participants (Leucht et al., 2013). Selection bias may be an issue in that people who are recruited to antipsychotic-free or minimal medication studies may be less symptomatic than those with more acute conditions who require hospitalisation, limiting the generalisability of our findings. For example in Morrison et al (2014) the antipsychotic-free participants had lower symptom severity at baseline than those

found for people with schizophrenia entering acute drug trials (Howes, 2014; Ogasa et al., 2013). In the Soteria study by Ciompi et al., (1992) severely unwell people were excluded from the study as they required hospital admission. Another concern is that in the largest and most influential psychodynamic psychotherapy study by May and colleagues, the therapists were not properly trained (May et al., 1981; May and Tuma, 1964). In another large study of psychodynamic psychotherapy, the therapy was provided for a much shorter length than is usual (mean=7 weeks) (Gottlieb et al., 1951) - given that this therapy is generally provided long-term (6 months-1 year+). Therefore neither of these studies may reflect best practice.

In a number of studies participants entering the antipsychotic-free group had their antipsychotic abruptly discontinued (Carpenter.,1977; Carpenter et al., 1990, 1987; Hogarty et al., 1974a). This may have inflated relapse rates as abrupt discontinuation may lead to withdrawal related relapse or deterioration potentially as a result of dopamine receptor supersensitivity (Moncrieff, 2006; Murray et al., 2016). Some older studies may also have used higher doses of antipsychotics than usual for the control groups. In these cases antipsychotic discontinuation could have been more beneficial due to the side-effect burden at higher doses. Although of the 7 studies (Carpenter, 1977; Ciompi et al., 1992; Cullberg et al., 2002; Hogarty and Goldberg, 1973; Karon and Vandenbos, 1972; May et al., 1981; Mosher and Menn, 1979) that provided information on baseline or maintenance group medication doses, none used 'high dose' antipsychotics as currently defined (> 1000mg chlorpromazine equivalents) (Royal College of Psychiatrists, 2014). Hence results in those who received psychosocial interventions are unlikely to be simply due to improvements following reduction of high dose medication.

Study quality was generally low which may have been due in part to the age of the papers and poor data reporting. For example, the standardisation of RCT reporting was only formalised in 1996 (Begg et al., 1996), which is later than the publication of all but two of the included trials (CBT). Data reporting and analysis were also weak, as although we attempted to recalculate effect sizes, the majority of studies did not report the pre and post-means and standard

deviations required to do this accurately and therefore we often used endpoint scores. There was a lack of clarity in the reporting of intent-to-treat analysis and power calculations, all of which may have introduced bias. There was also little information in many of the papers about how interventions were standardized and quality assured. Relapse was defined in a number of different ways across the studies (hospitalisations, symptomatic deteriorations), meaning that standardisation of reporting was difficult. This is in line with the lack of consensus on the definition of relapse across trials of antipsychotic medication (Gleeson et al., 2010). Lastly all of the authors of the included studies were proponents of the interventions they tested, which may have introduced bias.

4.2 Future research and conclusions

Although nine different psychosocial interventions have been studied, the overall evidence supporting the effectiveness of these interventions is generally weak. More RCTs of these psychosocial approaches are needed. This research would mean that people could be advised on the effectiveness of psychosocial treatments with and without antipsychotics, allowing them to make a more informed choice about the treatment they receive.

Examination of the main characteristics of the interventions did not reveal a consistent pattern of similarities or differences across the interventions. Future studies could explore the characteristics of these interventions in greater depth, assessing not only their descriptions and manuals, but investigating the actual practice of these treatments and what patients experience in the different interventions. This may require detailed qualitative research and should result in better identification of the commonalities and differences of the promising interventions, and might lead to the development of better specified and more effective interventions in the future. Finally, most of the included interventions are time-limited, whilst psychosis or schizophrenia can be on-going, and antipsychotics are often prescribed long-term. If psychosocial interventions are regarded as an alternative to antipsychotics over longer periods of time,

interventions may require further development for long-term use, and studies need to assess patient adherence and long term outcomes.

It is of note that we did not find any empirical studies with minimal or no antipsychotics for the Talking with Voices approach (Corstens et al., 2012) or in Hearing Voices Groups (Corstens et al., 2014). These approaches are growing in their use and go against traditional medication-focused treatments by engaging with the symptoms of psychosis as meaningful experiences. More research into these approaches is required, particularly in minimally or unmedicated people where they could potentially be trialled as alternatives to antipsychotics.

Evidence-based treatments should be available for people who do not wish to take antipsychotics, or wish to take the minimal amount. Our review has shown that nine different psychosocial interventions have been studied for people with schizophrenia or psychosis who are either unmedicated or receiving an antipsychotic minimisation strategy. The majority of studies reported outcomes for the intervention which were the same as the control group and there were some more encouraging findings for CBT, Need Adapted Treatment, and Soteria. However, study quality was problematic and there has been little recent research. As emphasised by the NICE guidelines, more high quality RCTs looking at the effectiveness of psychosocial treatments for people who do not wish to take antipsychotics or wish to take the minimal amount are required.

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Table 1

Characteristics of included studies

Study (country)	Design, follow-up, Setting (intervention duration (M))	Sample, age, N	Antipsychotic strategy	Outcomes[a]
CBT				
Morrison et al., (2012) (UK)	Exploratory (phase II) study (no control) 9, 15 months Outpatient (M=16.7 sessions)	Schizophrenia, schizoaffective disorder, delusional disorder (chronic and early intervention), mean age 26.8 years N=20	Participants had either stopped taking antipsychotics for at least 6 months while still experiencing symptoms, or had never taken antipsychotics	**Primary outcome** 1. Symptoms of psychosis **Secondary outcomes** 1. Dimensions of psychotic experience 2. Recovery 3. Social functioning
Morrison et al., (2014) (UK)	Randomised controlled trial 3, 6, 9, 12, 15, 18 months Outpatients (26 weekly sessions + 4 booster sessions)	Schizophrenia, schizoaffective disorder, delusional disorder (chronic and early intervention), mean age 31.3 years. Intervention N=37 Control N=37	**Intervention + control**: All participants had either stopped taking antipsychotics for at least 6 months while still experiencing symptoms, or had never taken antipsychotics.	**Primary outcome** 1. Symptoms of psychosis **Secondary outcomes** 1. Dimensions of psychotic experiences 2. Recovery 3. Social functioning 4. Emotional distress
Morrison et al., (2018) (UK)	Randomised controlled trial 6, 12, 24, 52 weeks Outpatients (26 weekly sessions + 4 booster sessions)	First episode psychosis, 2 people had multiple episode psychosis. Intervention N=26, antipsychotics N=24, antipsychotics + CBT N=25	Prior to randomisation participants had been antipsychotic free for at least 3 months. **Intervention:** did not receive antipsychotics Antipsychotics/antipsychotics+ CBT: received antipsychotics as usual	**Primary outcomes** 1. Feasibility 2. Symptoms of psychosis **Secondary outcomes** 1.Depression and anxiety 2.Quality of life 3. Social functioning 4.Recovery 5.Clinical global impression of symptom severity and improvement
Psychosocial (outpatient) treatment				
Carpenter, Douglas, Heinrichs, & Hanlon,	Randomised controlled trial	Schizophrenia, schizoaffective disorder, recent episode of	**Intervention:** Intermittent medication - drug free until	**Primary outcome:** Function **Secondary outcomes:** 1.

Study (country)	Design, follow-up, Setting (intervention duration (M))	Sample, age, N	Antipsychotic strategy	Outcomes[a]
(1987) (USA)	6 months, 1, 1.5, and 2 years Outpatient psychiatric clinics (2 years)	psychosis (number of episodes unspecified), mean age 31 years Intervention N=21 Control N=21	symptoms appear, stabilised on drugs (for ~ 4-6 weeks) then drug free again. **Control:** Continuous antipsychotic medication	Psychiatric symptoms, 2. Function, 3. Quality of life, 4. Hospitalisation rate, 5. Medication
Carpenter et al., (1990) (USA)	Randomised controlled trial 6 months, 1 year, 18 months, 2 years Experimental and control: Outpatient psychiatric clinics (2 years)	Patients who had had a recent episode of psychosis (number of episodes unspecified), mean age 28.1 years. Intervention N=57 Control N=59	**Intervention:** Intermittent medication - drug free until symptoms appear, stabilised on drugs (for ~ 4-6 weeks) then drug free again. **Control:** Continuous antipsychotic medication	**Primary outcome** Function **Secondary outcomes** 1. Psychiatric symptoms, 2. Quality of life, 3. Frequency of hospitalisation, 4. Decompensations, 5. Medication
Psychoanalysis/ psychodynamic psychotherapy				
Messier, (1969) (USA)	Randomised controlled trial 1 year, 3 years Experimental and control: Inpatient (2 years)	Schizophrenia (chronic - hospitalised for ≥ 3 years), mean age 27.2 years Intervention N=20 Control N=21	**Intervention:** Placebo **Control:** Antipsychotics	1. Psychopathology 2. Adjustment to the ward environment 3. Adjustment (combined: employment, recreation, and living status) 4. Symptoms of psychosis 5. Readiness for discharge
Karon & Vandenbos, (1972) (USA)	Randomised controlled trial 6, 12, and 20 months Inpatient and outpatient units (20 months)	Schizophrenia (chronic and first episode), 16-49 years. Intervention N= 9 Control N= 12	**Intervention:** Not taking antipsychotics **Control:** Antipsychotics only	1. Cognition, 2. Clinical evaluation of function, 3. Length of hospitalisation, 4. Measurement of thought disorder
May et al., (1976, 1981) (USA)	Randomised controlled trial 1, 2, 3, 4, and 5 years from admission.	Schizophrenia (first admission), age not specified. Intervention N=46,	**Intervention:** Unmedicated with antipsychotics **Control:** Medicated with	1. Length of time in hospital, 2. Success/failure index of hospital stay, 3. Psychiatric symptoms, 5. Employment, 6. Social function, 7.

Study (country)	Design, follow-up, Setting (intervention duration (M))	Sample, age, N	Antipsychotic strategy	Outcomes[a]
	And 3 months, 6 months, 1, 2, 3, 4, and 5 years from discharge Inpatient (0.5-1 year)	antipsychotics only N=48, psychodynamic + antipsychotics N=44, ECT N=47, Milieu N=43	antipsychotics (drug only, psychodynamic+drug), or unmedicated (ECT, milieu therapy)	Relationships, 8. Forensic history, 9. Suicide, 10. Personality and psychopathology
Gottlieb & Huston (1951)	Controlled trial (allocation method is unclear) Discharge, 6 months, 1, 2, 3, 4 years Inpatient (mean=7 weeks, range=1-27 weeks)	Schizophrenia,(first episode and chronic) mean age=26.5 years Intervention N=128 ECT N=143 Insulin therapy N=65	All participants were unmedicated	1.Social recovery, 2. Clinical improvement or no improvement
General Inpatient Milieu				
May et al., (1976, 1981) (USA)	Randomised controlled trial 1, 2, 3, 4, and 5 years from admission. And 3 months, 6 months, 1, 2, 3, 4, and 5 years from discharge Inpatient (0.5-1 year)	Schizophrenia (first admission), age not specified. Intervention N=43, Psychodynamic only N=46, antipsychotics only N=48, psychodynamic + antipsychotics N=44, ECT N=47.	**Intervention:** unmedicated with antipsychotics **Control:** medicated with antipsychotics (drug only, psychodynamic+drug), or unmedicated (ECT, psychodynamic only)	1. Length of time in hospital, 2. Success/failure index of hospital stay, 3. Psychiatric symptoms, 5. Employment, 6. Social function, 7. Relationships, 8. Forensic history, 9. Suicide, 10. Personality and psychopathology
Major Role Therapy				
Hogarty et al (1973, 1974a, b) (USA)	Randomised controlled trial Discharge from hospital, intake to outpatient clinic, 1, 2, 6, 12, 18, and 24 months Outpatient clinics (2-3 years)	Schizophrenia (first episode and chronic), 18-55 years. Intervention N=95 Antipsychotics only N=97 Placebo only N=87 Drug + MRT N=95	**Intervention:** placebo **Control:** 1. Antipsychotics only, 2. Placebo only, 3. Antipsychotics + Major role therapy	1. Relapse, 2. Time until relapse, 3. Quality of community adjustment
Soteria				
Cohort 1: Mosher & Menn, (1979); Matthews, Roper, Mosher, & Menn, (1979); Mosher, Menn, & Matthews, (1975)	Cohort 1: Quasi-experimental, consecutive assignment to experimental or control, Cohort 2: Randomised controlled trial	Schizophrenia (42%) or schizophreniform disorder (58%) with no more than 1 previous admission, mean age 21.7 years	**Intervention:** Antipsychotics not used for 6 weeks, prescribed after this if resident shows no change **Control:** Antipsychotics	1. Readmission, 2. Global psychopathology, 3. Global improvement, 4. Living independently or with peers, 5. Employment status, 6. Social

Study (country)	Design, follow-up, Setting (intervention duration (M))	Sample, age, N	Antipsychotic strategy	Outcomes[a]
Cohort 2: Mosher, Vallone, & Menn, (1995) **Cohort 1 and 2** Bola & Mosher, (2003) (USA)	Discharge, 1 month, 6 months, 1 year, 2 years Intervention: Soteria House (~6 months) Control: Inpatient wards of the community mental health	 Cohort 1: 79 (intervention N=37, control N=42) Cohort 2: 100 (intervention N=45, control N = 55)	primary treatment	functioning, 7. Composite score of 1-6
Ciompi et al., (1991, 1992, 1993) (Switzerland)	Randomization constrained by bed availability (quasi-experimental study) Discharge (experimental only), 2 years (case/control only) Intervention: Soteria House (5 months) Control: Inpatient hospital wards	Recent (≤ 1 year) onset schizophrenia/ schizophreniform psychosis, 17-35 years. Intervention N=22 Control N=22	**Intervention:** Antipsychotics used if no signs of improvement after 3-4 weeks or if danger to self or others. **Control:** Antipsychotics primary treatment	1. Global outcome (psychopathology, living situation, occupational situation), 2. Psychopathology 3. Housing situation 4. Employment status 5. Global autonomy (legal responsibility, living situation, job/financial situation, recreational activities, and social contacts) 6. Relapse rate 7. Treatment cost 8. Antipsychotic dose
Need Adapted Treatment				
Lehtinen, Aaltonen, Koffert, Räkköläinen, & Syvälahti, (2000) (Finland)	Controlled cohort study 2 years Experimental: Inpatient/ outpatient clinics (Not specified) Control: Inpatient wards	First episode psychosis (schizophrenia, schizophreniform psychosis, delusional psychosis, unspecified psychosis), mean age: 28.7 years. Experimental N=84, Control N=51	**Intervention:** Antipsychotics not used for 3 weeks, prescribed after this if no improvement **Control:** Antipsychotics as usual (immediately medicated)	1. Total time spent in hospital, 2. Symptoms of psychosis, 3. Employment status, 4. Global Assessment Scale (GAS) score, 5. Grip on life assessment (maintained/at least partly lost)
Cullberg, Levander, Holmqvist, Mattsson, & Wieselgren, (2002) Cullberg et al., (2006) (Sweden)	Controlled cohort study 1 year, 3 years Intervention: Inpatient/ outpatient clinics (not specified,	First episode psychosis mean age 28.4 years Experimental N=253 Control (historical) N=71 Control (prospective) N=64	**Intervention:** Antipsychotics not used for 1-2 weeks, given at lowest optimal dose if no improvement **Control:** Historical – antipsychotics as usual	1. Function, 2. Symptoms of psychosis, 3. Psychiatric symptoms, 4. Suicide, 5. Satisfaction with care, 6. Employment, 7. Disability allowance/sick leave, 8. Inpatient

Study (country)	Design, follow-up, Setting (intervention duration (M))	Sample, age, N	Antipsychotic strategy	Outcomes[a]
	varied) Control: Two inpatient/outpatient controls: 1. Historical control: clinics before participating in the study. 2. Prospective control: a clinic in Sweden			days, 8. Medication, 9. Cost, 10. Rorschach test
Open Dialogue				
Seikkula et al., (2003) (Western Lapland)	Controlled cohort study 2 years Intervention: Inpatient/ outpatient clinics (2 years) Control: Clinic which did not deliver need adapted treatment according to protocol	First-episode non-affective psychosis, mean age 27.7 years Experimental N= 23 Control N=14	**Intervention:** Antipsychotics not used for 3 weeks, prescribed after this if no improvement **Control:** antipsychotics provided immediately	1. Relapse rate, 2. Employment status, 3. Psychiatric symptoms, 4. Global functioning, 5. Schizophrenia prognosis.
Seikkula, Alakare, & Aaltonen, (2011) (Western Lapland)	Non-controlled cohort study 2 years Inpatient/outpatient clinics	First episode non-affective psychosis, mean age 20.2 years. N=18	Antipsychotics not used for 3 weeks, prescribed after this only if no improvement	1.Relapse, 2. Employment, 3. Psychiatric symptoms, Function, 4. Prognosis.
Psychosocial (inpatient) treatment				
Carpenter et al., (1977) (USA)	Observational study 1 year Intervention: Clinical research unit (3.8 months) Control: Inpatient hospital ward using antipsychotics as usual	Schizophrenia (undergoing a psychotic episode and 'generally' more than one episode), mean age 26.3 years Experimental N=49 Control N=73	**Intervention:** Aim was for patients to be drug free although antipsychotics could be used if necessary **Control:** Antipsychotics were the primary treatment	1. Mean outcome scores: combined score of work function, social function, time spent in hospital during the year, symptoms

a. The majority of studies did not specify whether outcomes were primary or secondary. Note. Symptoms of psychosis (e.g. positive/negative symptoms and general psychopathology), dimensions of psychotic experience (e.g. severity, distress and disability)

Table 2

Summary of quality scoring for randomised (using the Cochrane Collaboration's tool for assessing risk of bias) and non-randomised studies (using the Effective Public Health Practice Project (EPHPP) Tool)

Non-randomised studies (EPHPP)	**Strong**	**Moderate**	**Weak**
Domain			
Selection bias	3	4	2
Study design	4	5	0
Confounders	5	0	4
Blinding	0	2	7
Data collection methods	6	0	3
Withdrawals and drop-outs	3	5	1
Randomised studies (Cochrane tool)	**Low risk**	**Unclear risk**	**High risk**
Random sequence generation	4	4	0
Allocation concealment (selection bias)	2	6	0
Blinding of participants and personnel (performance bias)	0	3	5
Blinding of outcome assessment (detection bias)	4	2	2
Incomplete outcome data (attrition bias)	2	2	4
Selective reporting (reporting bias)	7	0	1

Table 3

Results from controlled studies for the effect of the no/low medication intervention on relapse (and/or length of hospital stay for inpatient studies), symptoms, and function.

Study	Intervention, N	Control, N	Relapse (symptomatic or hospitalisation)/length of hospital stay	Symptoms	Function
Cognitive Behavioural Therapy (CBT)					
Morrison et al (2014)	CBT, N=37	Treatment as usual (unmedicated), N=37	Number of people hospitalised during study period: Int=5, control=4 Deteriorations[g] during the study: Int=2, control=2	PANSS total: MD=-6.52, 95%CI -10.79 to -2.25, *p*=0.003[a]	Social function – Personal and Social Performance Scale: Est=5.47, *p*=0.04[a]
Morrison et al (2018)	CBT, N=26	Antipsychotics only, N=24	Number of people hospitalised during the study: Int=2, control=0 Deteriorations[h] during the study: Int=1, control=2	PANSS total: NS	Social function – Personal and Social Performance Scale: NS
Psychosocial outpatient treatment					
Carpenter et al (1987)	Psychosocial outpatient treatment, N=21	Antipsychotics only, N=21	Number of people hospitalised during study period: Int=11, control=9 RR=1.16, 95% CI 0.62-2.19[b]	BPRS total: NS	Level of Functioning Scale: NS
Carpenter et al (1990)	Psychosocial outpatient treatment, N=57	Psychosocial outpatient treatment + continuous	Number of people hospitalised during study period: Int=30, control=21	BPRS total: NS	Level of Functioning Scale: *p*<.01[b]

Study	Intervention, N	Control, N	Relapse (symptomatic or hospitalisation)/length of hospital stay	Symptoms	Function
		antipsychotic medication, N=59	RR=1.48, 95% CI 0.97-2.26[b] Deteriorations during the study[i]: MD=1.46, 95% CI 0.30-2.62[b]		
Psychoanalysis and psychodynamic psychotherapy					
Messier et al (1969)	Psychoanalytic psychotherapy + placebo, N=20	Antipsychotics only (in a local state hospital), N=21	Not measured	Quantified Mental Status (indicates a general level of symptoms): NS	Modified General Adjustment Planning Scale (measures employment, recreation, living status): NS
Karon & Vandenbos (1972)	Psychoanalytic psychotherapy (experienced therapist), N=3	Antipsychotics only, N=12	Length of hospitalisation: Shorter than control (p<.05)[a] Rehospitalisation: fewer rehospitalisations than control, 2 years after end of treatment (p<.05)[a]	Not measured	Clinical evaluation of function: better function in group receiving psychotherapy from an experienced therapist (p<.05)[a]
May et al (1976, 1981)	Psychodynamic psychotherapy, N=46	Antipsychotics only, N=48	Mean length of stay in hospital (from baseline admission till 3 year follow-up)[c]: Int: 395 days, Control: 225 days[b] Days of rehospitalisation for patients who were successfully discharged (3 year FU): NS	Menninger Health Sickness Scale 2 years post-discharge: MD= -5.8, 95% CI -9.99 to -1.6[b]	Proportion of time working for pay for participants discharged (2 years post-discharge): Antipsychotic only group spent longer working for pay MD=-1.10, 95% CI=-1.78 to -0.42[b] Social workers ratings of relationships and overall adjustment (2 years post-

Study	Intervention, N	Control, N	Relapse (symptomatic or hospitalisation)/length of hospital stay	Symptoms	Function
					discharge): 'psychotherapy alone were the lowest rank…the drug alone group was the highest…the drug effect was generally not significant'
Gottlieb & Huston (1951)	Brief psychodynamic psychotherapy, N=128	ECT, N=143	Mean length of hospitalisation: Int: 7 weeks, control: 9 weeks (significance is unreported)	Improvement and no improvement: NS	Complete and social recovery: NS
General inpatient milieu					
May et al (1976, 1981)	Milieu, N=43	Antipsychotics only, N=48	Mean length of stay in hospital (from baseline admission till 3 year follow-up)[c]: Int: 345 days, Control: 225 days[b] Days of rehospitalisation for patients who were successfully discharged (3 year FU): NS	Menninger Health Sickness Scale: NS	Proportion of time working for pay for participants discharged (2 years post-discharge): NS Social workers ratings of relationships and overall adjustment (2 years post-discharge): NS
Major Role Therapy (MRT)					
Hogarty et al (1973, 1974)	Major Role Therapy, N=95	Antipsychotics only, N=97	Relapse rates (deterioration) over 2 years study period[d]: MRT+placebo: 78%, Antipsychotics only: 53%[b]	Data unavailable for total sample	Data unavailable for total sample
Soteria					

Study	Intervention, N	Control, N	Relapse (symptomatic or hospitalisation)/length of hospital stay	Symptoms	Function
Bola & Mosher[e] (2003)	Soteria House USA, N=179 (total sample), N=63 (schizophrenia subgroup)	Antipsychotics as usual on an inpatient ward, N=97	Number of people readmitted during study period: total sample and schizophrenia subgroup: NS	Global psychopathology Scale: total sample: NS; Schizophrenia subgroup: Int had better global psychopathology and more improved psychopathology (Est=.34, p<.05)	Total sample - Social function: NS Employment: NS Living alone or with peers Est=0.18, *p*<.05[a] Schizophrenia subgroup: Social function: Int had better social functioning (Est=0.64, p<.05) Employment: NS Living alone or with peers: NS
Ciompi et al (1991, 1992, 1993)	Soteria Berne, N=22	Antipsychotics as usual on an inpatient ward, N=22	Relapse rate[j]: NS	BPRS total: NS	Housing situation: NS Employment: NS
Need Adapted Treatment					
Lehtinen et al (2000)	Need Adapted Treatment, N=84	A centre that was involved in Open Dialogue but organised treatment in a more institutional way and prescribed antipsychotics immedicately, N=51	Less than 2 weeks in hospital during study period, Int=50.8%, Control=25.6%, *p*=0.01[a]	No psychotic symptoms according to the CPRS during the last follow-up year: NS	Engagement in paid employment: NS Global Assessment Scale score 7 or more: Int=49.2%, control=25%, *p*=0.02[a] Maintained 'grip on life': NS
Cullberg et al (2006)	Need Adapted Treatment, N=253 (1 year),	Historical control: clinics before participating in the	1 year: Mean number of nights spent in overnight care: NS	1, 3 years: Not measured	1 year: Global Assessment Scale: Sig better in the intervention (p<.05, figures

Study	Intervention, N	Control, N	Relapse (symptomatic or hospitalisation)/length of hospital stay	Symptoms	Function
	N=61 (3 years)	study – antipsychotics as usual, N=71 (1 year), N=41 (3 years).	3 years: Mean number of nights spent in overnight care: NS		not provided).[a] 3 years: Global Assessment Scale: *d*=0.97, 95% CI 0.93-1.01[a] Receiving disability allowance: Int=38%, control=59%, *p*<.05[a]
Open Dialogue					
Seikkula et al (2003)	Open Dialogue, N=23	A centre that was involved in Need Adapted Treatment but organised treatment in a more institutional way and prescribed antipsychotics immedicately, N=14	Number of relapsed[f] patients Int: 6/23 (26%), Control: 10/14 (71%)	BPRS total: NS	Global Assessment Scale: Int /Control baseline: M=2.8(SD 0.64)/4.2(0.89), FU: 5.7 (1.3)/4.9 (1.6) Employment status, Number of people studying or working: Int: 15/23 (65%), Control: 3/14 (21%)
Psychosocial (inpatient) treatment					
Carpenter et al (1977)	Psychosocial (inpatient) treatment, N=49	Antipsychotics as usual on an inpatient ward, N=73	Mean outcome scores (combined scores of function, time spent in hospital, symptoms): MD: 1.6, 95% CI 0.32-2.88[a]		

Int=Intervention group, a. Significantly favours intervention (*p*<.05), b. Significantly favours control (*p*<.05), NS=No difference between intervention and control (*p*>.05).

c. Estimated from Figure 1 in May et al (1976);[9] d. Estimated from the figure in Hogarty et al,[12] statistical analysis of the difference in relapse rates between MRT+placebo and antipsychotics only is not reported in the paper. Relapse was defined as a clinical deterioration of such magnitude that re-hospitalisation was imminent; e. The paper reports three different analyses: endpoint, completers, and completers adjusted – we report data from 'endpoint' as this most closely reflects the 'intent-to-treat' analysis that is preferentially reported in trials; f. defined as 'making a new contact for

treatment after terminating the original treatment, or an intensification of existing treatment in the form of more intense meetings because of new psychotic or other symptoms'. g. Defined as >50% in adjusted PANSS total scores. h. Defined as > 25% deterioration in PANSS scores at the 6-week assessment or > 12.5% deterioration in PANSS scores at the 12-week assessment. i. Defined as a worsening in a patient's functioning and/or symptoms, as judged by the primary therapist and research psychiatrist. J. Defined as rehospitalisation, partial rehospitalisation or if a relative said the patient had a clear relapse.

PANSS=Positive and Negative Syndrome Scale,[20] Personal and Social Performance Scale,[21] BPRS=Brief Psychiatric Rating Scale,[22] Level of Functioning Scale,[23] Global Assessment Scale,[24] Global psychopathology Scale (7-point measure, 'not at all ill' to 'most extremely ill'),[25] Social function – used the social functioning subscale of the Brief Follow-up Rating,[26] CPRS=Comprehensive Psychological Rating Scale,[27] Grip on Life Assessment,[28] Quantified Mental Status,[29] Modified General Adjustment Planning Scale,[30] Menninger Health Sickness Scale,[31] Symptom Rating Scale.[32]

Table 4

Comparison of the main characteristics of the psychosocial interventions

Intervention	Individual sessions	Group sessions	Residential	Family involvement	Social network development / involvement	Employment rehabilitation	Therapeut-ic milieu[1]	Peer Support	Aims to reduce staff/client hierarchies	Long-term (>1 year)	Psycho-education	Practical support[2]	Multimodal approach[3]	Positively changing cognitive and social biases	Greater focus on internal factors[4]	Greater focus on external factors[5]	Manu-alised model
Cognitive Behavioural Therapy (CBT)	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Psychosocial (outpatient) treatment	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No
Pyschodynamic /psychoanalytic psychotherapy	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No
General inpatient milieu	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No
Major role therapy	Yes	Yes	No	No	Yes	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	No
Soteria	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No
Open Dialogue and Need Adapted Treatment[7]	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No
Psychosocial (inpatient) treatment	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	Yes[6]	Yes[6]	No
Total (%)	100%	75%	38%	38%	63%	38%	38%	12.5%	25%	63%	25%	50%	50%	13%	38%	75%	13%

1. A therapeutic environment (e.g. general nursing care, ward meetings, recreational activities); 2. Support with daily activities, such as shopping, managing finances; 3. Involves a number of different therapeutic approaches and therapists/staff e.g. family involvement and individual therapy sessions; 4. Greater focus on internal factors to treat the mental health problem, such as managing emotions, changing cognition; 5. Greater focus on external factors to treat mental health problems, such as improving social, family relationships, employment rehabilitation; 6. Equal focus on internal and external; 7. Open Dialogue was developed from Need Adapted Treatment, as such the core principles are similar and have been combined.

Table 5

Summary of results from controlled studies for the effect of the no/minimal antipsychotic intervention on relapse (and/or length of hospital stay for inpatient studies), symptoms, and function.

Outcome	**Better than control (N studies)**	**No difference (N studies)**	**Poorer than control (N studies)**	**Mixed results due to multiple measures (N studies)**
Relapse (hospitalisation)	1	4	2	-
Relapse (symptomatic)	0	0	1	-
Relapse (symptomatic+ hospitalisation)	1	1	1	-
Length of hospital stay	0	-	2	-
Symptoms	1	10	1	-
Function	4	6	1	3
Total	**7**	**21**	**8**	**3**

Note. Subsample analyses are not included

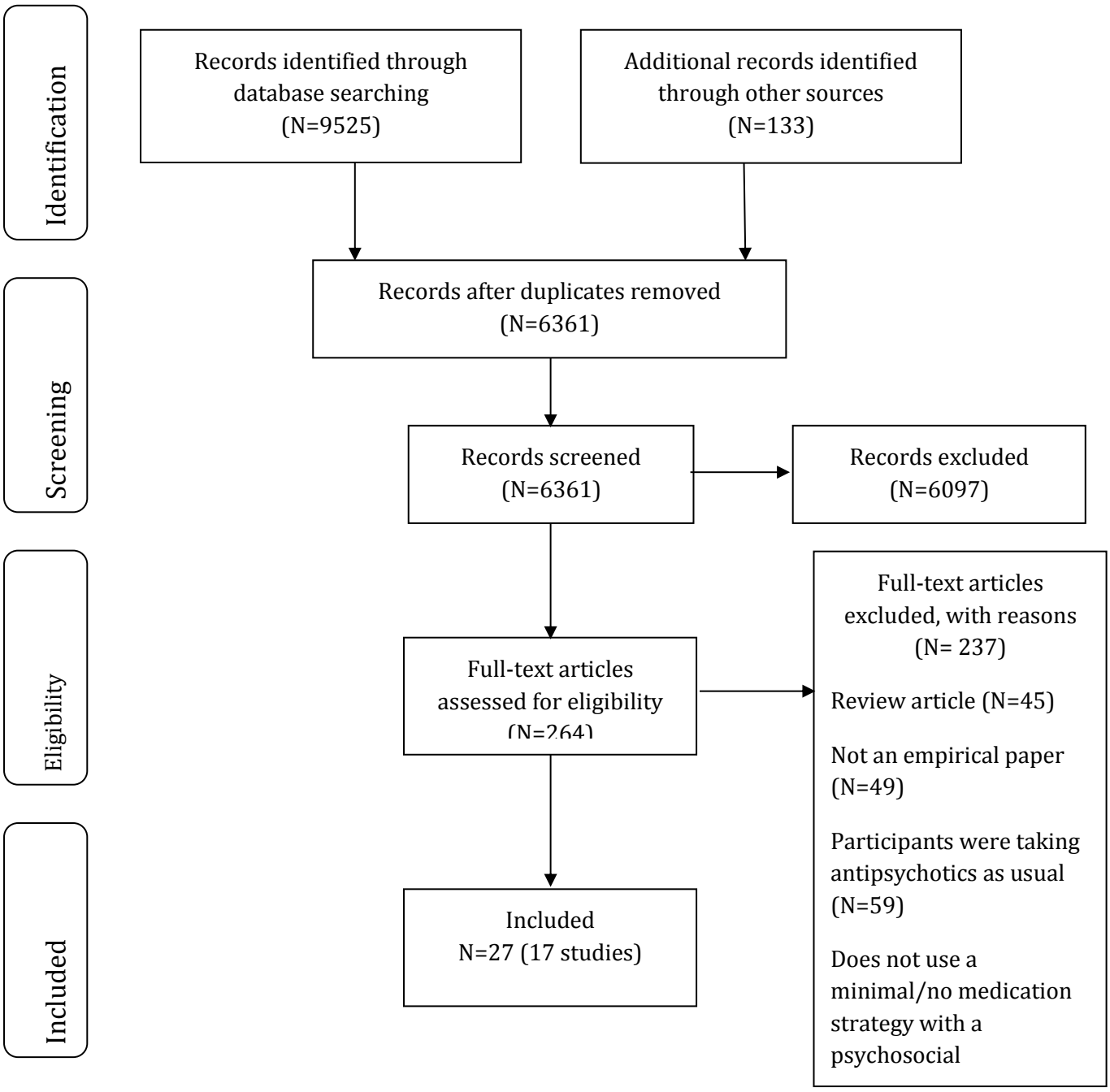

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram