Citation for published version (APA):
Abstract

Cognitive Behavioral Therapy (CBT) is recommended as a psychological intervention for those diagnosed with schizophrenia. The prevalence of auditory hallucinations is high among this group, many of whom are cared for by community mental health teams that may not have easy access to qualified CBT practitioners. This systematic review examined the evidence for the superiority of CBT compared to non-specialized therapy in alleviating auditory hallucinations in community patients with schizophrenia. Two RCTs met the inclusion criteria totaling 105 participants. The Positive and Negative Syndrome Scale (PANSS) – Positive Scale was the outcome measure examined. A meta-analysis revealed a pooled mean difference of -0.86 [95% CI -2.38, 0.65] in favor of CBT, although this did not reach statistical significance. This systematic review concluded there is no clinically significant difference in the reduction of positive symptoms of schizophrenia when treated by CBT compared to a non-specialized therapy for adults experiencing auditory hallucinations.

Keywords: schizophrenia, cognitive behavioral therapy, meta-analysis, systematic review
Introduction

Schizophrenia continues to affect approximately 1 in 100 people, with two thirds of this population going on to experience recurrent psychotic episodes (McGrath et al. 2008, Mental Health Foundation 2015). The prevalence of auditory hallucinations as a symptom of schizophrenia occurs in up to 50% of patients after their first psychotic episode, even with the introduction of antipsychotic medication (Zanello et al. 2014). Auditory hallucinations is used here to refer to a broad range of auditory percepts, including but not limited to speech (Waters and Jardri 2015). This can lead to distressing and negative experiences for individuals resulting in low mood and self-esteem, non-compliance with medication, lack of motivation, social isolation and harm to self and others (Shawyer et al. 2003, Wykes et al. 2005, Smith et al. 2006). For community mental health teams, supporting patients who experience auditory hallucinations is vital in order to promote and sustain recovery from illness.

In the United Kingdom (UK) and internationally, clinical practice guidelines (Dixon et al. 2010, NICE 2014) recommend Cognitive Behavioral Therapy (CBT) at various stages in the presentation of schizophrenia. However, in recent years the efficacy of CBT for the overall symptoms of schizophrenia has been questioned (Jones et al. 2011, Jauher et al. 2014, McKenna and Kingdon 2014). Jauher et al. (2014) argued that CBT for schizophrenia has been oversold as a psychological intervention as a result of unreliable and inconsistent data interpretation, weak methodological rigor and positive publication reporting bias. Furthermore, a Cochrane systematic review by Jones et al. (2011) found that there was no significant difference in the effectiveness of CBT when compared to psychosocial interventions for preventing relapse or re-admission into hospital, improvement of mental state and the management of positive and negative symptoms. That review, however, was limited by low quality and small-scale research and is no longer up to date.

A recent report (Thomas et al. 2014) from the International Consortium on Hallucinations Research concluded that while psychological therapies can be broadly effective for people with positive symptoms, more research is required to understand specific applications of therapies to voices. They note that therapies for auditory hallucinations, such as CBT, can require advanced levels of therapy skill and this can be a barrier to widespread dissemination. Therefore, they recommended the development of interventions that can be suitable for delivery in more routine service contexts such as in the community.

Non-specialized therapy is characterized by collaboration with a patient and can be found in interventions such as befriending, psycho-education and supportive therapy. Unlike CBT, these interventions contain skills and
resources that can be reproduced by the general community mental health teams (Buckley et al. 2007, Krakvik et al. 2013). The significance of such an intervention lies in that it will make it possible to support a patient in the community over a greater length of time when compared for example to the recommended 16 one-hour CBT sessions by the National Institute for Health and Care Excellence (2014). This longer-term approach could be more beneficial and sustainable for this specific patient population. However, currently there is limited research and data to explore the potential role and effectiveness of such interventions for community patients with schizophrenia and persistent auditory hallucinations (Buckley et al. 2007).

Krakvik et al. (2013) noted that current research into CBT interventions does not reflect the capabilities of a general mental health team as it employs well-trained and highly motivated CBT therapists. Reproducing this into current clinical practice has proven to be difficult. Recent findings from a North West Mental Healthcare Trust in England state that only 6.9% of community patients with schizophrenia were offered CBT (Haddock et al. 2014). These concerns are further supported by earlier reports of the difficulty in implementing CBT services into clinical practice (Berry and Haddock, 2008). Therefore, the current systematic review and meta-analysis seeks to examine the evidence for the superiority of CBT compared to non-specialized therapy in alleviating auditory hallucinations in community patients with schizophrenia.

**Methods**

This review was conducted following standard systematic review methodology and PRISMA reporting guidance (Moher et al. 2009, Higgins and Green, 2011). Relevant papers were searched for using the EMBASE (1980 to Week 17 2015), MEDLINE (1946 to April Week 3 2015) and PsycINFO (1806 to April Week 3 2015) databases. A systematic search was devised and applied in all the databases (Table 1). A scoping search was performed within the Cochrane Library of Systematic Reviews and the reference lists of relevant articles were scanned for additional papers. Further electronic searches were carried out on Web of Science, EU Clinical Trials Register, ClinicalTrials.gov (U.S. National Institutes of Health) and International Clinical Trials Registry Platform.
A randomized controlled trial (RCT) limit was used to ensure papers of the highest research quality. The inclusion criteria consisted of adults with schizophrenia/schizoaffective disorder residing in the community with no ongoing medication or symptomatic concerns. The recruited participants must have had a recent history or an on-going presence of auditory hallucinations and being treated with anti-psychotic medication. We excluded studies that focused on first-onset psychosis, acute settings and compared CBT to simply 'treatment as usual'; it had to be explicit that CBT was used for auditory hallucinations and the comparison group had to comprise of a non-specialized therapy. Studies were considered if their intervention design incorporated recognizable CBT techniques and non-specialized therapy focused on supportive interactions and social integration. No publication date or publication status restrictions were imposed.

The search results were filtered in an unblinded manner by the first author (LK) based on a review of titles, abstracts and full text (Figure 1). The first author (LK) performed data extraction following a standard template and the second author (AX) checked the extracted data. The studies were assessed for risk of selection, performance, attrition and detection bias\textsuperscript{19}. The meta-analysis was performed by computing the mean difference (MD) of the PANSS positive subgroup scale using a random effects model; this was facilitated by Review Manager 5 (RevMan). Heterogeneity and inconsistency were assessed (Q, \( I^2 \)). Both authors certify responsibility for the manuscript and declare no known conflicts of interest.
Figure 1: Exclusion flowchart

Results

The combined search of EMBASE, MEDLINE and PsycINFO yielded 119 papers with 38 duplicates. Of the 81 remaining papers, 73 were excluded due to irrelevance or not meeting the inclusion criteria. Of the eight papers read in full, six papers were excluded because: they did not have a 'non-specialized therapy' as comparison (n=3; Wykes et al. 2005, Thomas et al. 2011, Zanello et al. 2014); did not recruit participants with a recent history or an on-going presence of auditory hallucinations, or being treated with anti-psychotic medication (n=1; Trower et al. 2004); the research was undertaken in an inpatient rather than community setting (n=1; Valmaggia et al. 2005); and, one paper (n=1; Klingberg et al. 2010) was a protocol for a study yet to be completed. Finally, two papers met the inclusion criteria and were included in the meta-analysis. A gap in appropriately powered RCTs was revealed through this search, which may reflect a known general difficulty with recruiting people with
schizophrenia into research (Thornley and Adams, 1998). There is also a lack of RCTs that include an active comparison that could be defined as a non-specialized therapy (Buckley et al. 2007).

Penn et al. (2009) and Shaywer et al. (2012) were the two studies that met the inclusion criteria for this review; both studies are single assessor-blind RCTs with a combined sample size of 105 (Table 2). Participants were recruited through outpatient services and undertook similar screening processes so the participant characteristics within and between studies did not vary extensively. Both studies formulated an intervention that included recognizable CBT techniques and detailed the need for a controlled comparison that would best reflect treatment in an outpatient environment. The Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) was used by both studies as a secondary outcome measure to quantify the impact upon participants’ positive psychotic symptoms. It should be acknowledged that participants were recruited from outpatient environments where they were stable in mental state and so the results can mainly be generalizable towards a population in remission, rather than those in crisis care.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Evidence Level</th>
<th>Number of Subjects</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Follow-up</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn et al (2009)</td>
<td>Single Assessor-blind RCT</td>
<td>Level II</td>
<td>n = 65</td>
<td>Recruitment: Outpatient referrals from primary clinicians in central North Carolina, USA Male 51% Average Age 40.65 Years of Education 12.75 IQ 93.6</td>
<td>Group CBT n = 32 12x 1 hour weekly sessions, covering: +Intro to treatment +Psycho-education +Content of AH +Behavioural analysis of AH +Increasing &amp; decreasing strategies for AH +Coping strategies for AH</td>
<td>Supportive Therapy n = 33 12 week – Manual based intervention +Establish therapeutic alliance +Agreeing on interpersonal goals (within group) +Focussing on social integration +Emotional support +Counselling of non-symptom related problems</td>
<td>3 month &amp; 12 month</td>
<td>PANSS* Positive Score</td>
<td>-0.346</td>
<td>Treatment trials grant from the Stanley Foundation</td>
</tr>
<tr>
<td>Shawyer et al (2012)</td>
<td>Single Rater-blind RCT using part-parallel group comparison design involving the intervention and comparison condition.</td>
<td>Level II</td>
<td>n = 43</td>
<td>Recruitment: Private and public mental health services in Victoria, Australia Male 59% Average Age 39.8 Years of Education 11.9 IQ 99.6</td>
<td>‘Torch’ CBT n = 20 15 x 50 minute weekly sessions, covering: +Engagement &amp; assessment +Belief modification +Acceptance-based Interventions Motivational +interviewing +Personalised psycho-education +Enhancing self-efficacy +Relapse prevention +Coping assertion +Termination</td>
<td>Befriending n = 20 15 week – Manual based control intervention +Sessions focus on neutral topics of interest and enjoyment of the client +Such as hobbies, sports &amp; current affairs +Explicit avoidance of symptom discussion (redirected to clinician) +Provide the rationale for treatment &amp; positive expectancy</td>
<td>6 month</td>
<td>PANSS* Positive Score</td>
<td>-0.029</td>
<td>Grants from the National and Medical Research Council of Australia &amp; the Rebecca L Cooper Medical Research Foundation. Therapist training funded by grants from Novartis Pharmaceuticals Australia Pty Ltd and Eli Lilly Australia Ltd</td>
</tr>
</tbody>
</table>

* Positive and Negative Syndrome Scale
Risk of bias within studies

There was low risk of selection bias due to the distance between research personnel and the act of sequencing and allocating participants to their interventions. However, Shawyer et al. (2012), unlike Penn et al. (2009), chose not to stratify by gender, which may account for the distribution imbalance between male/female within interventions. They did not refer to this imbalance within their discussion, yet it may be a slight weakness in deducing generalizability to the greater population. In both studies, the authors explain and detail how they have made steps to overcome performance bias indicating good reporting although not eliminating risk of bias.

Detection bias was countered in both studies by creating independent blind roles, for example blind rater/assessor, thus decreasing the risk of bias. However, Penn et al. (2009) stated ‘experimental blindness’ was used by asking the research assistants, participants and study therapists not to talk about the treatment. This statement does not clarify whether Penn et al (2009) actually accounted for this vulnerability and does not explain the consequences of such breaches. Shawyer et al. (2012) stated that breaches of blindness occurred 22 times across 97 assessments and raters were replaced in five instances.

Risk of attrition bias was also low because dropout rates were <5% across the studies suggesting that missing data would not impact significantly on the final results. However, both studies were not explicit in how they dealt with their missing data and this lack of transparency introduces a level of bias. The low attrition level suggests that all the interventions used in the studies were tolerable by participants.

Overall, both studies implemented actions in order to limit risk of bias, especially in relation to specific difficulties that arise from a talking therapy intervention, and were transparent in their reporting. However, both studies included areas that lacked clarity and left the reader to assume what the action may have been.

Synthesis of results

Individual study results are included in Figure 2. End-of-treatment outcome data were available from both trials and used for the analysis, reporting data for a total of 105 patients (CBT = 52; non-specialized therapy=53).

The pooled analysis showed no statistically significant difference in the reduction of positive symptoms between CBT and non-specialized therapy (MD -0.86, CI -2.38-0.65, p=0.26). Although the pooled mean point estimate
(-0.86) falls in favor of a CBT intervention, the pooled estimate confidence interval (-2.38, 0.65) crosses the line of no effect.

Cochran’s Q (0.6871, p=0.4071) suggested that statistical heterogeneity was insignificant as did the I² value of 0%. It is worth noting that true heterogeneity may not have been uncovered as Q has low power as a comprehensive test of heterogeneity especially when the number of studies is small (Gavaghan et al. 2000).

The CBT interventions lowered the PANSS positive subscale score by an average of 0.86 points further than a non-specialized therapy. With a maximum score of 49 on the positive subscale score, 0.86 suggests a clinically insignificant difference between the two interventions.

The quality of the body of the evidence used in this systematic review was assessed following the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al. 2011a) (Table 3). While the papers have a low risk of bias, no serious inconsistency or indirectness, there is serious concern for imprecision (Guyatt et al. 2011b). The relatively wide confidence intervals in comparison to the similar mean differences and small sample sizes suggest definite imprecision across the data. Therefore, the quality of the overall body of evidence is downgraded to ‘moderate’ (Guyatt et al. 2011a).
Table 3: GRADE profile

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cognitive Behavior Therapy</th>
<th>Non-specialised Therapy</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shawyer et al. 2012</td>
<td>14.5 [3.7]</td>
<td>14.6 [3.9]</td>
<td>-0.10 [-2.46, 2.26]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>52</td>
<td>53</td>
<td>-0.86 [-2.38, 0.65]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.69, df = 1 (p = 0.41); i^2 = 0%$
Test for overall effect: $z = 1.12 (p = 0.26)$

Reduction in positive psychotic symptoms (PANSS Positive Score; range of scores: -3.0 - 3.0; Improvement indicated by lower values)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Penn et al. 2009; Shawyer et al. 2012.</em></td>
<td>52</td>
<td>53</td>
<td>MD -0.86 (-2.38 lower to 0.65 higher)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. The wide confidence interval introduces concern over imprecision.
2. The evidence support recent studies suggesting that there may be no significant difference in improvement in the overall symptoms of schizophrenia using a CBT intervention compared to a non-specialized therapy.
Discussion

Our analysis was limited by examining one outcome measure (PANSS) within two studies. The selected data was taken at the post treatment phase, thus not considering data found at the follow-up phase. However, the two studies were specifically designed for those affected by auditory hallucinations which differ from previous systematic reviews that had a broader focus on the overall symptoms of schizophrenia in their target population (Jones et al. 2011, Jauher et al. 2014). The current systematic review was limited by inherent time and cost restrictions and so grey literature could not be thoroughly searched. We also acknowledge that the databases searched represent research written in English and therefore important papers written in other languages could have been missed; although, no abstracts were excluded based on language.

The results of recent systematic reviews and meta-analyses that have examined the efficacy of CBT produced conflicting recommendations (Jones et al. 2011, Jauher et al. 2014, van der Graag et al. 2014). In a recent paper Thomas et al. (2014) argued that existing RCTs show that psychological interventions such as CBT broadly improve participants’ positive symptoms but lack the flexibility to explore the successful therapeutic methods and processes, and are limited in their ability to adjust to the varying needs of participants and of service delivery. Their vision for future treatment of auditory hallucinations includes a varied list of interventions such as mindfulness-based therapy, technology-based therapy such as avatar programs, peer support and shared lived experiences. The results of the current systematic review support Thomas et al.’s (2014) vision and therefore we recommend the conduct of further, larger and adequately powered RCTs examining the use of non-specialized therapy as a long-term supportive measure, especially within mental health community teams.

Conclusion

The current systematic review and meta-analysis is based on a moderate quality body of evidence that confirms no clinically significant difference in the reduction of positive symptoms of schizophrenia when being treated by CBT compared to a non-specialized therapy. We detected no harmful effects of either intervention upon participants and so the continued recommendation for CBT in the treatment of schizophrenia, auditory hallucinations in particular, is not disputed. However, our results add weight to the conclusions of others (Jones et al. 2011, Thomas et al. 2014) that CBT may not be superior to other psychosocial interventions at least in the context of community mental health. Practitioners working with patients with Schizophrenia should explore
individual client needs and preferences in order to consider the benefits of non-specialized therapies and services more readily available in the community. Based on our results, we join the calls of others and urge policymakers to support a multi-therapy service approach to the treatment of schizophrenia with auditory hallucinations in the community, which includes but is not exclusive to CBT.
References


