CBT Versus Standard Care for Schizophrenia

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COMMENTARY ON… COCHRANE CORNER

Summary

Whilst antipsychotic medication remains the mainstay of treatment for schizophrenia, in isolation, these medications are not always successful. Cognitive Behavioural Therapy ('CBT') is recommended as an adjunct to pharmacological treatment. The Cochrane review under consideration evaluates the effects of offering CBT as an add-on to standard care versus standard care alone, with this commentary putting those findings into their clinical context.

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Declaration of Interest None

Introduction

Cognitive Behavioural Therapy ('CBT') is founded upon the theory that there exists a relationship between a person's thoughts, feelings, and behaviour. Originally developed for the treatment of depression, its use has since expanded to include treatment for a broad number of mental health problems. Since the 1990s, it has also attracted increasing interest as a treatment for patients with psychotic disorders. CBT for schizophrenia aims to help the individual to normalise and re-evaluate their psychotic experiences, and thereby changes behaviours and reduces symptom-related distress and impact on functioning (NICE, 2014).

Although medication remains the primary treatment for schizophrenia, up to a quarter of patients continue to exhibit symptoms despite the use of medication (Meltzer, 1992). The latest guidelines from the National Institute for Health and Care Excellence (NICE, 2014) for the treatment of psychosis in adults recommend that all patients exhibiting a first episode and subsequent acute episodes of psychosis should be offered individual CBT in conjunction with oral antipsychotic medication. This recommendation was driven by a clinical review of 31 randomised controlled trials ('RCTs') (N = 3052) in which CBT was reviewed, with 'any alternative management treatment' as the comparator (NICE, 2014).

However, the National Clinical Audit of Psychosis (Royal College of Psychiatrists, 2018) found that only 36% of patients had been offered CBT of any kind and only 26% were offered a specific form of CBT for psychosis ('CBTp'). Of those offered CBTp, the offer was taken up by 52% of patients.

Summary of the Cochrane Review

The Cochrane review by Jones *et al* (2018) includes 60 RCTs (N = 5 992) involving patients diagnosed with schizophrenia or related disorders. It compares adding CBT to standard care with standard care alone. The results suggest the addition of CBT has no effect on long-term risk of relapse, mental state, social functioning, and quality of life, although it may have some effect on improving long-term global state and reducing the risk of adverse events. The strength of these conclusions was limited by the poor quality of available evidence.

BOX 1 'Standard Care'

Standard care is also known as treatment-as-usual ('TAU'), usual care, or routine care. Standard care is often used as a control condition in RCTs to determine whether the addition of a new intervention is a significant improvement on current practice (Freedland *et al*, 2011). It can be a useful design to inform policy-making.

However, what standard care involves for a particular condition may vary significantly (e.g. between countries and over time) and is often not well-defined (Burns, 2009). The quality of standard care may vary, or in fact be several different interventions. This variation can make it difficult to conclude whether or not a significant result is due to an effective intervention or poor quality standard care. It can also lead to heterogeneity, i.e. inconsistency, across studies.

Definition of the clinical question

The review aimed to assess whether the addition of CBT to standard care had measurable effects on a range of primary and secondary outcomes. The population were patients with a current diagnosis of schizophrenia or closely related illnesses such as schizoaffective disorder and schizophreniform disorder.

RCTs that randomly allocated people with a current diagnosis of schizophrenia or closely related illness to receive either CBT plus standard care or standard care alone were selected. Studies with participants with very late onset schizophrenia were excluded. If studies randomised people with a large range of diagnoses, they excluded trials where fewer than 50% of the participants had a diagnosis of schizophrenia or closely related illness.

Single-blind trials were included. A sensitivity analysis was applied to trials that did not include a blinding procedure to test whether there was a significant difference in outcome measures compared with single-blind trials – if not, the non-blinded trials were included. Quasi-randomised trials were excluded. Data from cross-over trials were included only up to the point of first cross-over to avoid carry-over effects of treatments.

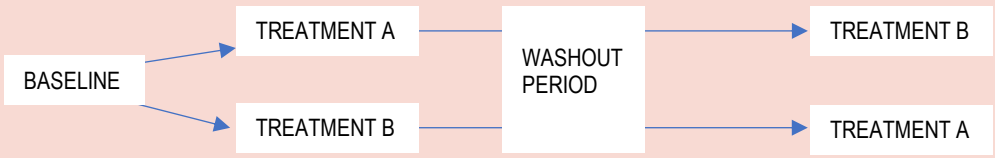
BOX 2 Crossover trials

In a crossover trial, subjects cross over from one treatment to another treatment during the course of the trial, rather than remaining on one treatment throughout the trial as in a parallel trial design.

An advantage of crossover trials is that subjects essentially act as their own controls, allowing the response of a patient to Treatment A to be compared to that same patient's response to Treatment B. This removes within-patient variation and also means that crossover trials require a smaller population while achieving the same level of statistical power.

However, there is the potential for carryover effects, whereby the residual effects of the treatment in the first phase influence the response to the treatment in the second phase, thus distorting the results. This is particularly problematic with treatments that are not quickly reversible. A 'washout period' between treatments aims to minimise these effects (Sibbald, B., and Roberts, C. 1998).

In this review, by only using data from cross-over trials prior to crossover, carryover effects are avoided.



The review establishes a clear definition of its authors' view of 'well-defined CBT', as focussing on belief change or re-evaluation of the subjective meaning of symptoms, with any studies which fell outside of this definition (or were ambiguous) included as 'less-well-defined CBT', and thereafter subject to a sensitivity analysis against the primary outcomes measures compared with those studies using well-defined CBT.

Standard care involved only antipsychotic treatment in 12 of the trials, but also included a broader biopsychosocial approach and use of mental health services in the remaining studies.

Types of outcome measures were grouped into two primaries (Global State, subdivided into relapse and clinically important change; Mental State) and eight secondaries (Global State; Mental State; Adverse Effects; Functioning; Quality of Life; Satisfaction with Treatment; Engagement with Services; and Economic).

These outcomes were assessed as defined in the individual studies using various definitions and rating scales; relapse generally referred to an exacerbation of symptoms, variously defined, with a duration criterion of either 1 or 2 weeks, and/or leading to a change in management such as an increase in medication. Clinically important change in global state referred, for example, to being 'much improved' on the clinical global impression improvement ('CGI-I') scale or a 50% reduction in score on a specified rating scale e.g. BPRS or CGI severity scale. Over 30 different rating scales were used to measure mental state outcomes. Outcome results were grouped into short-term, medium-term, and long-term, but the authors were primarily interested in long-term outcomes, defined as over 52 weeks since the onset of therapy.

Method

The search strategy used the Cochrane Schizophrenia Group's Trials Register, which is compiled from systematic searches of the major electronic databases (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.gov, Embase, MEDLINE, PsycINFO, PubMed, WHO IC-TRP), and registries of clinical trials, as well as grey literature and conference proceedings, with no restrictions as to language, date of publication, or publication status. The references of identified studies were then scrutinised for any further relevant studies.

The search initially returned 1802 records and following screening by the authors 60 trials were included with a total of 5992 participants. Two authors independently reviewed the citations yielded by the search, identifying the most relevant abstracts. A randomised 20% sample of the proceeds of this were then re-inspected by two different review authors to check for consistency of results. If the groups of review authors did not agree, the full study was then reviewed to settle the issue by further discussion.

A GRADE approach was used to assess the certainty of the evidence (Schunemann, 2013). Risk of bias was assessed by two review authors using the Cochrane Handbook of Systematic Review of Interventions criteria. Where disputes arose, two other review authors acted as adjudicators. Where sequence generation was judged to be at a high risk of bias, or where there was no attempt to conceal allocation, studies were excluded.

The statistical analysis of data used relative risk (RR) for binary data and mean difference (MD) for continuous data, all with 95% confidence intervals (CIs).

BOX 3 Relative Risks and Mean Differences

Relative risk (RR) is the same as a risk ratio. Risk is defined as the number of events divided by the total number of participants. RR is the ratio of the risk of an event in the intervention group relative to the risk of the event in the control group. RR does not provide information about the absolute risk, but tells you how likely an event is in the intervention group relative to the control group (Tenny and Hoffman, 2019).

$$RR = \frac{\text{risk of event in the intervention group}}{\text{risk of event in the control group}}$$

A RR of <1 means the risk of an outcome is reduced by the intervention. A RR >1 means the risk of the outcome is increased by the intervention. A RR =1 means there is no difference between the two groups.

Mean difference (MD) is the 'difference in means'. It measures the difference between the mean value in the two groups. It is an estimate of how much, on average, an intervention changes the outcome compared to the control (Higgins and Green, 2011).

Results

There was no clear difference between the CBT and standard care arms for reducing long-term risk of relapse (RR 0.78, 95% CI 0.61 to 1.00), or for long-term improvement in mental state (RR 0.81, 95% CI 0.65 to 1.02), social functioning (MD 0.56,

95% CI -11.32 to 4.12), quality of life (MD -3.60, 95% CI -11.32 to 4.12), or satisfaction with treatment (RR 0.93, 95% CI 0.77 to 1.12).

Only two trials provided usable data for each of the outcomes of long-term improvement in global state (Grawe, 2006; Wang, 2015) and long-term risk of any adverse events (Li, 2014; Pan 2012), but these data showed that adding CBT to standard care could be better for long-term improvement in global state (RR 0.57, 95% CI 0.39 to 0.84) and reducing the risk of adverse events (RR 0.44, 95% CI 0.27 to 0.72). None of the trials reported data for economic outcomes of direct and indirect costs of care.

The quality of the evidence for the relapse outcome was assessed to be 'low' due to heterogeneity and large confidence intervals that included both appreciable harm and benefit. The evidence for the global state, mental state, adverse events, social functioning, and quality of life was even further downgraded to 'very low' due to issues with high or unclear risk of bias (in areas such as blinding, random sequence generation, and allocation concealment), small sample size, low number of events, and indirectness of outcome measures. The evidence for the satisfaction with treatment outcome was considered to be of moderate quality, having been downgraded for using participants leaving the study early for any reason ('drop-out rate') as a proxy for satisfaction with treatment, which is a rather crude indicator.

Overall, the clinical significance of these findings is difficult to interpret given the low quality of the evidence underpinning them.

BOX 4 Low number of events

Results are considered imprecise for binary (dichotomous) outcomes when there are a low number of events. As a result of few events there may be large confidence intervals around the effect estimate, because the influence of extreme values will be more significant.

Discussion

In summary, this Cochrane review showed no clear advantage for CBT plus standard care compared to standard care alone in terms of reducing long-term risk of relapse, or long-term improvements in mental state, social functioning, quality of life, or satisfaction with treatment. It may be better in terms of improvements in long-term global state and to reduce the risk of any adverse events. However, the quality of the evidence was generally very poor and there are a number of other limitations.

The trials may include unrepresentative groups of patients. The review included patients with schizophrenia and closely-related illnesses such as schizoaffective disorder and schizophreniform disorder but also included studies that had randomised a range of diagnoses (including delusional disorder and mood disorders), only excluding trials where fewer than 50% of participants had diagnoses of schizophrenia or similar illnesses. All but four of the studies included in the review had excluded participants with comorbid substance abuse (Barrowclough, 2001; Barrowclough, 2010; Barrowclough, 2014; Gleeson, 2009), an issue commonly encountered in the clinical population. The studies are also not clear on the extent to which personality factors may be prominent.

None of the included studies clearly described the severity of illness. Most excluded people with marked thought disorder or conceptual disorganisation. Overall RCTs tend to exclude those with the most severe psychopathology; the most severely ill are generally not well enough to consent to participate in a trial and those with high risks are generally excluded. This leaves a more moderate group that is not necessarily generalisable to a clinical population of, for instance, those who are not in remission despite antipsychotic treatment.

The average length of illness in studies varied from over one month to 30.1 years. Some of the studies included people who were in recovery from schizophrenia while others included patients with first episode schizophrenia, or with chronic schizophrenia. The authors had originally intended to do a subgroup analysis comparing those in a first episode of illness with those with a longer history but studies did not include enough information to carry out that analysis. It would also be interesting to examine whether there is a differential effect on positive and negative symptoms.

BOX 5 Subgroup analyses

Subgroup analyses involves splitting data into subgroups in order to compare them. They can be used to examine specific factors that might influence the effects of an intervention. These factors might be population characteristics (e.g. age, gender), types of intervention, or types of study. Subgroup analyses may also be able to explain some of the variability in results across studies (i.e. heterogeneity) (Higgins and Green, 2011).

The review considered only studies that compared CBT plus standard care to standard care alone. A comparison treatment, such as other psychosocial treatments, would better allow for an assessment of the efficacy of the specific modality of CBT - rather than simply whether it is better than what is already available and provided - by controlling for the extra therapeutic relationship. This question was addressed by another Cochrane review in this family (Jones *et al*, 2018b) in which they found no clear advantage of CBT over other psychosocial treatments, some of which were much less sophisticated than CBT such as 'befriending', or supportive counselling. However, again the strength of their conclusions was limited by the low quality of available evidence.

There was no assessment of the therapeutic relationship in these studies. Future studies could consider examining the role of the therapeutic alliance given that a number of meta-analyses have found a moderate, but reliable, association between a good therapeutic alliance and therapeutic success in both adult and youth psychotherapy (Hovarth and Symonds, 1991; Martin *et al.*, 2000; Karver *et* al, 2006), irrespective of the specific modality of therapy, and has also indicated that the patient's view of the therapeutic alliance may be a better predictor than is the therapist's view. It may be worth including an assessment of the patient's perspective on the relationship in future studies to assess how much of a role the quality of the therapeutic relationship plays. On a related note, the authors did examine whether therapist experience impacted on outcomes and found that after removing studies with inexperienced therapists there were no clear differences in results between CBT and standard care for primary outcomes, including global state improvement in the long-term. However, greater therapist experience or technical expertise does not necessarily equate to a stronger therapeutic relationship.

In terms of blinding, all trials were considered to have a high risk of performance bias since it is not possible to blind participants to treatment condition when they are required to actively engage in the therapy, and it is clearly very different to standard care. This means that there may unavoidably be some expectancy effects on the behalf of participants. Nevertheless, it is possible to blind the trialist collecting outcome data to treatment condition to avoid detection bias. 22 of the studies did not address whether outcome assessors were blinded leading to an unclear risk of bias. Three of the studies (Gumley, 2003; Kuipers, 1997; Startup, 2004) stated that the outcome assessors were not blinded, leading to a high risk of detection bias.

The authors had originally planned to examine the impact of the length of CBT treatment. The length of treatment ranged from 28 days in one study (He, 2012) to up to two years in others (Cao, 2014; Grawe, 2006). This analysis was abandoned and addressed in another Cochrane review (Naeem *et al*, 2015) that attempted to compare the effects of brief CBT (6 to 10 sessions) with standard CBT (12 to 20 sessions) for people with schizophrenia but found no studies comparing the two. In terms of external validity there is also a question of whether patients with schizophrenia in the clinical population will reliably attend all CBT sessions.

Only two trials included in this review reported rates for any adverse effects (Li *et al*, 2014; Pan, 2012), though others reported specific adverse events such as death, suicide attempts, and incidents of violence. Any intervention can cause unintended side effects and yet psychological interventions are sometimes assumed not to have any. Few studies consider the adverse effects of psychological therapies, which even when well-delivered may include dependency, increased distress, or strains in family relations *inter alia* (Schermuly-Haupt *et al*, 2018; Jones *et al*, 2018*)*.

There were a large number of different outcome measures for most of the primary outcomes. For mental state, for example, the trials in the review reported this outcome in 38 different ways. It would be helpful to reach a consensus about clinically

meaningful outcomes. The Clinical Global Impression ('CGI') severity and improvement scales were used by most studies that measured change in global state. However, the CGI scales are subjective assessments made on the basis of clinical judgement. In the CGI severity scale patients are rated from 1 ('normal, not at all ill') to 7 ('among the most severely ill) and scoring relies on the clinician having prior clinical experience. This subjectivity is likely to affect the reliability and validity as an outcome measure.

The trials did not provide information on anti-psychotic drug dosage and, therefore, there was no outcome that considered whether the addition of CBT may have allowed for a reduction in antipsychotic medication. Given the significant side effect burden of long-term anti-psychotic medication, a reduced dose or overall lower absolute dose of anti-psychotic medication could be a very meaningful outcome for patients.

Conclusions

This review (Jones et al, 2018) assessed the evidence for the use of CBT as an adjunct to standard care for schizophrenia, an approach that is advocated by NICE guidelines, compared to standard care alone.

In summary, the results of this review did not provide statistical evidence of an advantage of adding CBT to standard care in terms of reducing long-term risk of relapse or of long-term clinically important improvement in mental state, social functioning, or quality of life. There was some evidence that it may improve long-term global state and reduce the risk of adverse events.

However, there were significant limitations in the primary evidence and the strength of this review's conclusions was limited by the poor quality of available evidence.

Overall, it is questionable whether this review will influence clinical practice in the UK; however, it has highlighted some key questions that future research could explore further, and the authors have included a proposed study design that future RCTs could follow.

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