Is adjunctive CBT really effective for schizophrenia?

ROUND THE CORNER

Katherine Reid

COMMENTARY ON… COCHRANE CORNER[†]

SUMMARY

Although antipsychotic medication remains the mainstay of treatment for schizophrenia, medications alone 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 compared with standard care alone, and this commentary puts those findings into their clinical context.

DECLARATION OF INTEREST

None.

KEYWORDS

Schizophrenia; cognitive behavioural therapies; statistical methodology.

Cognitive–behavioural therapy (CBT) is founded on 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 attracted increasing interest as a treatment for people with psychotic disorders. CBT for schizophrenia aims to help the individual to normalise and re-evaluate their psychotic experiences, and thereby change behaviours and reduce symptom-related distress and impact on functioning (National Institute for Health and Care Excellence 2014).

Although antipsychotics remain the primary treatment for schizophrenia, up to one third of patients continue to exhibit symptoms despite their use (Lehman 2004). The latest guidelines on the treatment of psychosis in adults published by the National Institute for Health and Care Excellence (2014) 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 evaluated, with 'any alternative management treatment' as the comparator.

However, the National Clinical Audit of Psychosis (Royal College of Psychiatrists 2018: pp. 4–5) found that only 36% of patients with psychosis in England and Wales 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.

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 randomised controlled trials to determine whether the addition of a new intervention is a significant improvement on current practice (Freedland 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, and the treatments themselves may differ depending on the provider. This variation can make it difficult to conclude whether or not a significant result is due to an effective trial intervention or to poor-quality standard care. It can also lead to heterogeneity, i.e. inconsistency, across studies.

Summary of this month's Cochrane review

The review by Jones et al (2018a) in this month's Cochrane Corner includes 60 RCTs involving 5992 individuals diagnosed with schizophrenia or related disorders. It compares adding CBT to standard care (Box 1) with standard care alone. The results suggest that 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 in improving long-term global state and reducing the risk of adverse events. The strength of these conclusions was limited by the poor quality of the available evidence.

Definition of the clinical question

The review aimed to assess whether the addition of CBT to standard care had measurable effects on a

Katherine Reid is a core psychiatry trainee within Oxford Health NHS Foundation Trust in the south of England. She has an interest in research in the area of psychotherapy.

Correspondence Dr Katherine Reid, Warneford Hospital, Warneford Lane, Headington, Oxford OX3 3JX, UK. Email: katherine.reid@psych.ox.ac.uk

First received 30 Mar 2019
Accepted 11 Apr 2019

[†]See this issue.

https://doi.org/10.1192/bja.2019.26 Published online by Cambridge University Press

range of primary and secondary outcomes. The population was patients with a current diagnosis of schizophrenia or closely related illnesses, such as schizoaffective disorder or schizophreniform disorder.

Randomised controlled trials 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, the reviewers 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 (Box 2) was applied to trials that did not include a masking (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 (Box 3) were included only up to the point of first cross-over, to avoid carry-over effects of treatments.

The review establishes a clear definition of its authors' view of 'well-defined CBT', describing it as CBT focusing on belief change or re-evaluation of the subjective meaning of symptoms; any studies that fell outside of this definition (or were ambiguous) were subjected to a sensitivity analysis using the primary outcome data of the studies that employed well-defined CBT.

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

Types of outcome measure were grouped into two primaries (global state, subdivided into relapse and clinically important change; and 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 in the individual studies, using various definitions and rating scales; relapse generally referred to an exacerbation of symptoms, variously defined, for a duration 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 Impressions (CGI) Improvement scale or a 50% reduction in score on a rating scale such as the Brief Psychiatric Rating Scale (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 review authors were primarily interested in long-term outcomes, defined as over 52 weeks since the start of therapy.

BOX 2 Sensitivity analysis

Sensitivity analysis is when the primary analysis is repeated with a different data-set or statistical method. It is often used when an assumption or unclear decision has been made, for example when a primary study does not include the required information or when an arbitrary numerical cut-off is chosen. Examples in this review were the inclusion of studies that lacked a masking (blinding) procedure and those with 'less well-defined CBT'. In these examples the analysis was repeated without the data that were thought to be of lower quality to see whether that significantly changed the outcome estimate. If the outcome is robust then there will be little difference between the two (Higgins 2011).

BOX 3 Cross-over trials

In a cross-over trial, participants 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 cross-over trials is that participants essentially act as their own controls, allowing the response of a patient to treatment A to be compared with that same patient's response to treatment B. This removes within-patient variation and also means that cross-over trials require a smaller population while achieving the same level of statistical power.

However, there is the potential for carry-over 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 1998).

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

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

BJPsych Advances (2019), vol. 25, 273–278 doi: 10.1192/bja.2019.26

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 review 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 these abstracts 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 problem by further discussion.

The GRADE approach was used to assess the certainty of the evidence (Schünemann 2013: chapters 4 and 5). Risk of bias was assessed by two review authors using the Cochrane Handbook for Systematic Reviews of Interventions criteria (Higgins 2011). 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 (Box 4), all with 95% confidence intervals (CIs).

BOX 4 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 that event in the control group:

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

The 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 2019). An RR <1 means that the risk of an outcome is reduced by the intervention. An RR >1 means the risk of the outcome is increased by the intervention. RR = 1 means that 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 with the control condition (Higgins 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 0.61–1.00), or for long-term improvement in mental state (RR = 0.81, 95% CI 0.65–1.02), social functioning (MD = 0.56, 95% CI −2.64 to 3.76) and quality of life (MD = −3.60, 95% CI −11.32 to 4.12), or for satisfaction with treatment (RR = 0.93, 95% CI 0.77–1.12).

Only two trials provided usable data for the outcomes of long-term improvement in global state (Grawe 2006; Wang 2015) and long-term risk of any adverse events (Pan 2012; Li 2014), 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 0.39–0.84) and reducing the risk of adverse events (RR = 0.44, 95% CI 0.27–0.72). None of the trials reported data for the economic outcomes of direct and indirect costs of care.

The quality of the evidence for the relapse outcome was assessed to be 'low' owing 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 outcomes was even further downgraded to 'very low' because of high or unclear risk of bias (in areas such as masking (blinding), random sequence generation and allocation concealment), small sample size, low number of events (Box 5) 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.

Discussion

In summary, this Cochrane review showed no clear advantage for CBT plus standard care compared with 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

BOX 5 Low number of events

If there is a low number of events, results are considered imprecise for binary (dichotomous) outcomes. As there are few events there may be large confidence intervals around the effect estimate so that results are more influenced by extreme values.

satisfaction with treatment. It may be better in terms of improvements in long-term global state and reducing the risk of adverse events. However, the quality of the evidence was generally very poor and there are a number of other limitations.

Trial participants

The trials may include unrepresentative groups of patients. In addition to studies involving patients with schizophrenia and closely related illnesses, such as schizoaffective disorder and schizophreniform disorder, the review included studies that had randomised a range of diagnoses (including delusional disorder and mood disorders), only excluding such trials if 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 misuse (Barrowclough 2001, 2010, 2014; Gleeson 2009), a problem commonly encountered in the clinical population. There may also be an issue with diagnostic assessment in that it can be difficult to distinguish between those experiencing psychotic symptoms (hearing voices, paranoid ideation) in the context of borderline personality disorder from those with a psychotic illness (Kingdon 2010, D'Agostino 2019).

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 the studies varied from over 1 month to 30.1 years. Some of the studies included people who were in recovery from schizophrenia, whereas others included people with first-episode schizophrenia or with chronic schizophrenia. The review authors had originally intended to do a subgroup analysis (Box 6) comparing those in a first episode of illness with those with a longer history, but the studies did not include enough information to carry out that analysis. It would be interesting to examine the impact of CBT in different phases of the illness and, perhaps, also whether there is a differential effect on positive and negative symptoms.

BOX 6 Subgroup analysis

Subgroup analysis involves splitting data into subgroups in order to compare them. It 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 2011).

Therapist effects

The review considered only studies that compared CBT plus standard care with standard care alone. A comparison with 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 2018b), in which they found no clear advantage of CBT over other psychosocial treatments, some of which were much less sophisticated than CBT, for example 'befriending' and 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 itself 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 (Horvath 1991; Martin 2000; Karver 2006), irrespective of the specific modality of therapy, and have also indicated that the patient's view of the therapeutic alliance may be a better predictor than is the therapist's view. In future studies It may be worth including an assessment of the patient's perspective on the relationship to assess how much of a role the quality of the therapeutic relationship plays.

On a related note, the review authors did examine whether therapist experience influenced outcomes. They found that, after removing studies with inexperienced therapists, there were no clear differences in results between CBT and standard care for primary outcomes, including improvement in global state in the long term. However, greater therapist experience or technical expertise does not necessarily equate to a stronger therapeutic relationship.

Performance and detection bias

In terms of masking (blinding), all trials were considered to have a high risk of performance bias since it

BJPsych Advances (2019), vol. 25, 273–278 doi: 10.1192/bja.2019.26

is not possible to mask participants to treatment condition when they are required to actively engage in the therapy and it is clearly very different from standard care. This means that there may unavoidably be some expectancy effects on the behalf of participants. Nevertheless, it is possible to mask the trialist collecting outcome data to treatment condition, thus avoiding detection bias. Of the 60 studies, 22 did not address whether outcome assessors were masked, leading to an unclear risk of bias. Three studies (Kuipers 1997; Gumley 2003; Startup 2004) stated that the outcome assessors were not masked, leading to a high risk of detection bias.

Duration of treatment

The review authors had originally planned to examine the effect of the length of CBT treatment (treatment length ranged from 28 days in one study (He 2012) to up to 2 years in others (Grawe 2006; Cao 2014)), but they abandoned this analysis. An earlier Cochrane review (Naeem 2015) attempted to compare the effects of brief CBT (6–10 sessions) with standard CBT (12–20 sessions) for people with schizophrenia but found no studies comparing the two. In terms of the external validity of such an analysis, there is a question of whether people with schizophrenia in the clinical population will reliably attend all CBT sessions.

Adverse effects

Only two trials included in this review reported rates for any adverse effects (Pan 2012; Li 2014), although 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 result in, for example, dependency, increased distress or strains in family relations (Jones 2018a; Schermuly-Haupt 2018).

Outcome measures

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 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. On 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 rater having prior clinical experience. This subjectivity is likely to affect the scale's reliability and validity as an outcome measure.

Antipsychotic dose reduction as an outcome

The trials did not provide information on antipsychotic drug dosage and there was therefore 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 antipsychotic medication, a reduced dose or overall lower absolute dose of antipsychotic could be a very meaningful outcome for patients.

Conclusions

This review (Jones 2018a) 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 with standard care alone.

In summary, the results of the 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.

The review does not provide much evidence in support of current NICE guidelines. However, there were significant limitations in the primary evidence and the strength of the review's conclusions was limited by the poor quality of available evidence. The review authors have included a proposed study design that future RCTs could follow.

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.

Acknowledgements

The author would like to thank Dr Riccardo De Giorgi, Dr Olga-Maria Tsatalou and Dr David Geaney for their advice on this project. The views expressed here are the views of the author and not necessarily those of the National Health Service.

References

Barrowclough C, Haddock G, Tarrier N, et al (2001) Randomized controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *American Journal of Psychiatry*, **158**: 1706–13.

Barrowclough C, Haddock G, Wykes T, et al (2010) Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis

and comorbid substance misuse: randomised controlled trial. *BMJ (Clinical Research Edn)*, **341**: c6325.

Barrowclough C, Marshall M, Gregg L, et al (2014) A phase-specific psychological therapy for people with problematic cannabis use following a first episode of psychosis: a randomized controlled trial. *Psychological Medicine*, **44**: 2749–61.

Burns T (2009) End of the road for treatment-as-usual studies? *British Journal of Psychiatry*, **195**: 5–6.

Cao J, Zhu J, Xu L, et al (2014) Study on the effects of cognitive-behavioral intervention on the rehabilitation of first-episode schizophrenia. *Journal of Psychiatry*, **27**: 297–9.

D'Agostino A, Rossi Monti M, Starcevic V (2019) Psychotic symptoms in borderline personality disorder: an update. *Current Opinion in Psychiatry*, **32**: 22–26.

Freedland KE, Mohr DC, Davidson KW, et al (2011) Usual and unusual care: existing practice control groups in randomized controlled trials of behavioural interventions. *Psychosomatic Medicine*, **73**: 323–35.

Gleeson JFM, Cotton SM, Alvarez-Jimenez M, et al (2009) A randomized controlled trial of relapse prevention therapy for first-episode psychosis patients. *Journal of Clinical Psychiatry*, **70**: 477–86.

Grawe RW, Falloon IR, Widen JH, et al (2006) Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatrica Scandinavica*, **114**: 328–36.

Gumley A, O'Grady M, McNay L, et al (2003) Early intervention for relapse in schizophrenia: results of a 12-month randomized controlled trial of cognitive behavioural therapy. *Psychological Medicine*, **33**: 419–31.

He X, Li Z, Chen Y (2012) Efficacy of cognitive behavioral therapy for anxiety in females with first-episode paranoid schizophrenia. *Medical Journal of Chinese People's Health*, **24**: 651–3.

Higgins JPT, Green S (eds) (2011) Part 2: General methods for Cochrane reviews. In *Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0*. Cochrane Collaboration.

Horvath AO, Symonds BD (1991) Relation between working alliance and outcome in psychotherapy: a meta-analysis. *Journal of Counseling Psychology*, **38**: 139–49.

Jones C, Hacker D, Xia J, et al (2018a) Cognitive behavioural therapy plus standard care versus standard care for people with schizophrenia. *Cochrane Database of Systematic Reviews*, **12**: CD007964 (doi: 10.1002/14651858.CD007964.pub2).

Jones C, Hacker D, Meaden A, et al (2018b) Cognitive behavioural therapy plus standard care versus standard care plus other psychosocial treatments for people with schizophrenia. *Cochrane Database of Systematic Reviews*, **11**: CD008712 (doi: 10.1002/ 14651858.CD008712.pub3).

Karver MS, Handelsman JB, Fields S, et al (2006) Meta-analysis of therapeutic relationship variables in youth and family therapy: the evidence for different relationship variables in the child and adolescent treatment outcome literature. *Clinical Psychology Review*, **26**: 50–65.

Kingdon DG, Ashcroft K, Bhandari B, et al (2010) Schizophrenia and borderline personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia, and childhood trauma. *Journal of Nervous and Mental Disease*, **198**: 399–403.

Kuipers E, Garety P, Fowler D, et al (1997) London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. I: Effects of treatment phase. *British Journal of Psychiatry*, **171**: 319–27.

Lehman ALJ, Dixon L (2004) APA practice guidelines: Schizophrenia. *American Journal of Psychiatry*, **161**(Suppl 2): 1–56.

Li X, Guo Y, Fu C, et al (2014) Clinical efficiency and safety of CBT combined with low-dose risperidone alliance treatment on auditory hallucination in schizophrenia patients. *Sichuan Mental Health*, **27**: 502–4.

Martin DJ, Garske JP, Davis MK (2000) Relation of the therapeutic alliance with outcome and other variables: a meta-analytic review. *Journal of Consulting and Clinical Psychology*, **68**: 438–50.

Naeem F, Farooq S, Kingdon D (2015) Cognitive behavioural therapy (brief versus standard duration) for schizophrenia. *Cochrane Database of Systematic Reviews*, **10**: CD010646 (doi: 10.1002/14651858.CD010646.pub3).

National Institute for Health and Care Excellence (2014) 1 Recommendations. In *Psychosis and Schizophrenia in Adults: Prevention and Management* (Clinical Guideline CG178). NICE.

Pan S (2012) Cognitive therapy in the care of schizophrenic depression. *Xin Li Yisheng*, **7**: 206–7.

Royal College of Psychiatrists (2018) *National Clinical Audit of Psychosis: National Report for the Core Audit 2018*. Healthcare Quality Improvement Partnership.

Schermuly-Haupt M-L, Linden M, Rush AJ (2018) Unwanted events and side effects in cognitive behavior therapy. *Cognitive Therapy and Research*, **42**: 219–29.

Schünemann H, Brożek J, Guyatt G, et al (2013) *GRADE Handbook*. GRADE.

Sibbald B, Roberts C (1998) Understanding controlled trials: crossover trials. *BMJ*, **316**: 1719.

Startup M, Jackson MC, Startup S (2004) Insight and recovery from acute psychotic episodes: the effects of cognitive behavior therapy and premature termination of treatment. *Journal of Nervous and Mental Disease*, **194**: 740–50.

Tenny S, Hoffman MR (2019) *Relative Risk*. STATPearls Knowledge Base/ StatPearls Publishing (http://knowledge.statpearls.com/chapter/nurse-calculations/28324). Accessed 23 April 2019.

Wang Z, Guo Z, Han G, et al (2015) Efficacy of cognitive-behavioral therapy in community schizophrenia patients. *China Journal of Health Psychology*, **23**: 16–9.