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CBT for schizophrenia: a critical viewpoint

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In England and Wales, cognitive behavioural therapy (cognitive therapy, CBT) has been part of official treatment guidelines for schizophrenia since 2002 (NICE, 2002)(*Schizophrenia / Guidance and guidelines / NICE* n.d., p. 200). The 2014 NICE guideline (NICE, 2014)(*Psychosis and schizophrenia in adults: treatment and management / Guidance and guidelines / NICE* n.d.), which is based on the same meta-analytic evidence as its predecessor in 2009, recommends that it be offered to all people with schizophrenia, including first episode patients and those with established illness and patients who are actively symptomatic and in remission. Similar recommendations are to be found in the Scottish SIGN guideline (SIGN, 2013)(*SIGN 131 Management of schizophrenia* n.d.) as well as those of several other countries (Rathod *et al.* 2010).

In 2012, however, the Cochrane collaboration sounded a discordant note, concluding that ‘[t]rial-based evidence suggests no clear and convincing advantage for cognitive behavioural therapy over other – and sometimes much less sophisticated – therapies for people with schizophrenia’ (Jones *et al.*, 2012)(Jones *et al.* 2012). A further challenge came from a 2014 meta-analysis carried out by ourselves (Jauhar *et al.*, 2014)(Jauhar *et al.* 2014), which found end of treatment effect sizes that were uniformly in the small range (overall symptoms: 0.33 [95% CI 0.47 to 0.19], 34 studies; positive symptoms: 0.25 [95% CI 0.37 to 0.13], 33 studies; negative symptoms: 0.13 [95% CI 0.25 to 0.01], 34 studies) (*note* these and all further effect sizes are shown as a positive sign favoring CBT). A 2018 network meta-analysis of various psychological interventions to reduce positive symptoms in schizophrenia (Bighelli *et al.*, 2018), carried out on a rather different dataset of 27 studies than us, again found pooled effect sizes for CBT in the small range, though this time at the upper end of this (vs treatment as usual: 0.30 [95% CI 0.14 to 0.45], 18 trials; vs inactive control interventions: 0.29 [95% CI -0.55 to 0.03],

7 trials)(Bighelli *et al.* 2018). Most recently, a 2018 update of the 2012 Cochrane meta-analysis has continued to find no clear or convincing evidence of superiority on any measure apart from leaving the study early (Jones *et al.*, 2018).

In the wake of a ‘viewpoint’ article examining whether it is right to continue to regard CBT as a gold standard for depression and anxiety (Leichsenring & Steinert 2017), we consider the current status of this form of therapy in schizophrenia and the related psychotic disorders that are typically included in trials of it (schizoaffective disorder, delusional disorder and psychosis not otherwise specified). We draw on what can legitimately be regarded as the two best sources of evidence, namely meta-analyses and large, well-conducted individual trials.

Is CBT effective in high quality trials?

Figure 1 shows pooled effect sizes for positive symptoms, the class of symptoms that CBT was originally developed to treat, in meta-analyses carried out since 2001. **A fall over time is evident, with meta-analyses carried out in the last five years all finding pooled effect sizes in the small range (0.1-0.3). It seems likely that this reflects the larger sample sizes and increased attention to methodological factors that have tended to characterize more recent trials.**

[Insert Figure 1 here]

In our 2014 meta-analysis (Jauhar *et al.*, 2014), we found a significant moderating effect of blinding: the pooled effect size reduced from 0.33 to 0.15 (95% CI 0.03 to 0.27) in 20 trials of overall symptoms, and fell from 0.25 to non-significant levels (0.08 [95% CI 0.03 to 0.18] in 20 trials of positive symptoms)(Jauhar *et al.* 2014). Bighelli *et al.* (2018) had more nuanced results in their network meta-analysis: they found the small but

significant ES for CBT was maintained in blind studies when compared against treatment as usual (0.27, 95% CI: 0.13 to 0.41) but not against inactive control interventions (0.14, 95% CI: -0.09 to 0.37).

Of course, blinding is not the only measure that contributes to trial quality – others include randomization (especially allocation concealment, the taking of steps to ensure that the randomization code cannot be broken, typically by use of remote allocation) (Schulz & Grimes 2002a), and the use of measures to deal with incomplete outcome data (Schulz & Grimes 2002b). In **our meta-analysis** (Jauhar *et al.*, 2014) we addressed this broader issue by pooling data from studies that were rated as being at low risk of bias from all three of these factors. Effect sizes for overall and positive symptoms were small and non-significant in these studies (overall symptoms: 0.15 [95% CI -0.01 to 0.32], 8 studies; positive symptoms: 0.10 [95% CI -0.09 to 0.28], 9 studies) (Jauhar *et al.* 2014, p. 22014). However, pooling data only from trials deemed to be at low risk of bias not only severely restricts the study base but also depends on information given by authors about their methodology, which may be scanty, especially in older studies. In these circumstances, findings from a very large, methodologically rigorous, ‘definitive’ trial would be of considerable interest.

One such trial, the POSITIVE trial of Klingberg *et al.* (2010)(Klingberg *et al.* 2010), comes close to meeting these requirements. Begun in 2007, this aimed to recruit 330 people diagnosed with schizophrenia, schizoaffective disorder or delusional disorder, who were randomised to 9 months of CBT or an intervention designed to control for non-specific elements of therapeutic contact, supportive therapy. Randomization and blinding were state-of-the-art and analysis was planned to be by intention-to-treat.

Publication of this trial has been delayed (for details see (see Coyne:

<http://blogs.plos.org/mindthebrain/2016/02/23/effect-of-a-missing-clinical-trial-on->

what-we-think-about-cognitive-behavior-therapy (*Study of therapy for psychosis gone missing* 2016)), but is now anticipated to appear in the near future.

Is CBT effective against particular symptoms?

van der Gaag *et al.* (van der Gaag *et al.* 2014a) meta-analyzed 11 studies that separately examined outcomes for delusions and hallucinations, and which were also selected on the basis that they used individually tailored, case formulation-based CBT. The findings for delusions were not greatly different from those of **our** 2014 meta-analysis (Jauhar *et al.*, 2014) for positive symptoms: the pooled effect size was 0.36 in 9 studies, reducing to 0.24 in 6 blind studies. However, the effect size was noticeably larger for hallucinations, being 0.44 in 11 studies and, at 0.46, this value was maintained in 8 blind studies.

The same year saw publication of the COMMAND trial of Birchwood *et al.* (2014)(Birchwood *et al.* 2014), a large (N=197), 9-month trial of hallucination-adapted CBT compared to treatment as usual (TAU). This employed randomization by remote allocation, used multiple measures to prevent unblinding of assessors, and analysis was by intention-to-treat. The primary outcome was harmful compliance with voices: on this measure the CBT group showed significant superiority, although this was not seen at end of treatment (odds ratio [OR] 0.74, 95% CI 0.40 to 1.39) but became apparent at 18-month follow-up (OR 0.45, 95% CI 0.23 to 0.88). No significant effect on overall hallucinations severity was seen, however, at either time point, or on individual hallucination variables such as distress or frequency.

It seems increasingly clear that CBT is ineffective against negative symptoms. Velthorst *et al.* (2015)(Velthorst *et al.* 2015) found no significant effect in 28 trials of negative symptoms as a secondary outcome (effect size [ES] 0.09 [95% CI -0.03 to 0.21]), nor in two trials where negative symptoms were the primary outcome (ES 0.16 [95% CI -0.10 to 0.41]). One of these latter two trials (Klingberg *et al.*, 2011) was large (N=198), employed randomization by remote allocation, blinding and analysis by intention-to-treat. Importantly, the form of CBT used was also adapted to specifically target negative symptoms(Klingberg *et al.* 2011).

CBT for relapse

NICE found an effect of CBT on reducing hospitalization compared to treatment as usual in one of three meta-analyses examining this outcome carried out for the 2009 guideline (see: National Collaborating Centre for Mental Health: www.nccmh.org.uk). On the other hand, there was no evidence of effectiveness against relapse, when compared to either standard care (relative risk [RR] 0.85 [95% CI 0.50 to 1.41], 3 trials) or to other active treatments (RR 1.05 [CI 0.85 to 1.30], 4 trials).

Neither of these two latter meta-analyses included the large (N=218) trial of Garety *et al.* (2008)(Garety *et al.* 2008) of CBT vs treatment as usual. This examined relapse rates based on evidence of re-emergence of or significant deterioration in positive psychotic symptoms lasting at least two weeks. The trial employed blinding, randomization by remote allocation and analysis by intention to treat. Its results were negative, leading the authors to conclude generic CBT for psychosis was not indicated for relapse prevention in patients recovering from a recent episode of psychosis.

Is CBT more effective in treatment-resistant patients?

Burns *et al.* (Burns *et al.* 2014) meta-analyzed randomized trials of CBT in medication-resistant patients, finding apparently substantial end of treatment effect sizes of 0.52 (95% CI 0.35 to 0.70) in 12 studies of overall symptoms and 0.47 (95% CI 0.27 to 0.67) in 9 studies of positive symptoms. However, they used an unconventional measure of effect size (difference in change scores divided by end of treatment standard deviation) which does not permit their results to be quantified in terms of the widely used rule of thumb of small (0.1-0.3), medium (0.4- 0.7) and large (0.8+). Recalculation of the pooled effect size for their 9 studies of positive symptoms using a conventional metric (Hedges' *g*) gives an approximate result (values had to be estimated for one study) of 0.31 (95% CI 0.12 to 0.50) falling to 0.26 (95% CI 0.04 to 0.47) in 7 blind studies – not markedly different from the values found in **our** meta-analysis of the same year (Jauhar *et al.*, 2014)(Jauhar *et al.* 2014).

The recently published FOCUS trial (Morrison *et al.*, 2018)(Morrison *et al.* 2018)(*Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomised controlled trial - The Lancet Psychiatry* n.d.) examined effectiveness of CBT over a period of 9 months (plus later booster sessions) vs treatment as usual in 487 patients with clozapine-resistant schizophrenia. As well as being very large, this trial was well-conducted, employed randomization by remote allocation and assessor blinding (with measures taken to address accidental breaking), and analysis was by means of a modern equivalent of intention to treat (White *et al.*, 2011)(White *et al.* 2011). No significant effect was seen at the primary endpoint of 21 months (ES 0.06), but a small effect (ES 0.16) was noted at the end of the 9-month treatment period.

CBT: not a 'quasi-neuroleptic'?

More than a decade ago, Birchwood and Trower (Birchwood & Trower 2006) argued that treating CBT as a 'quasi-neuroleptic' is inappropriate and that the intervention is more likely to have a distinctive profile of effects that is complementary to drug treatment rather than substituting for it. Such a view finds echoes in UK clinical guidelines: NICE (NICE n.d.) emphasized not only effects on psychotic symptoms but also reduction of distress associated with symptoms, promotion of social and educational recovery and reduction of depression and social anxiety. Similarly, SIGN (2013)(SIGN 131 *Management of schizophrenia* n.d.) stated: 'The aim [of CBT] is to help the individual normalize and make sense of their psychotic experiences, and to reduce the associated distress and impact on functioning'.

Laws *et al.* (2018)(Laws *et al.* 2018) recently meta-analyzed these relatively understudied outcomes. In 27 trials that examined the effects of CBT on functioning, the pooled effect size was small at end-of-trial (ES 0.25 [95% 0.14 to 0.33]), although this became non-significant at follow-up (16 trials, ES 0.10 [95% CI -0.07 to 0.26]). A small-to-medium benefit on distress was found at end-of-treatment in 8 trials (ES 0.37, [95% CI 0.05 to 0.69]), which became non-significant when adjusted for possible publication bias (ES 0.18, [95% CI -0.12 to 0.48]). There was no evidence of an effect on quality of life in 10 trials (ES 0.04, [95% CI -0.12 to 0.19]).

Freeman *et al.* (2015) examined another non-core outcome, worry secondary to delusions, in a large trial. One hundred and fifty patients with schizophrenia, schizoaffective psychosis or delusional disorder who scored significantly on a worry

questionnaire were randomly assigned to 8 weeks of either worry-directed CBT or treatment as usual (Freeman *et al.* 2015). At both end of treatment and 24 weeks follow-up the CBT group showed significantly reduced worry scores (ES estimate common to both outcome points 0.47). This trial was generally methodologically robust, but it should be noted that worry was measured on a self-report scale and so could not be considered to have been evaluated under blind conditions.

Can CBT prevent transition to psychosis?

Hutton and Taylor (Hutton & Taylor 2014) meta-analyzed 6 trials of using CBT in individuals at risk of developing psychosis, and found evidence that it was effective in reducing the transition rate at 6, 12 and 18 months (6 months: RR 0.47 [95% CI 0.27 to 0.82], 6 studies; 12 months: RR 0.45 [95% CI 0.28 to 0.73], 6 studies; 18–24 months: RR 0.41 [95% CI 0.23 to 0.72], 4 studies). This meta-analysis included two large, well-conducted multicentre trials (N=288, Morrison *et al.*, 2012) and N=206, van der Gaag *et al.*, 2012); the former failed to find a significant difference in transition frequency but the latter found a significant (55%) reduction.

Interpretation of the findings in this area is complicated by a subsequent network meta-analysis that examined the effect of CBT and a range of other interventions (Davies *et al.*, 2018)(Davies *et al.* 2018). This found no significant effect of CBT on transition compared to standard clinical management. This meta-analysis excluded one of the two multicentre trials (van der Gaag *et al.*, 2012) included by Hutton and Taylor (2014)(van der Gaag *et al.* 2012), on the grounds that it used CBT enhanced with psychoeducation and metacognitive strategies. It also included two new studies: one of these was a relatively small trial (N=57) (Stain *et al.*, 2016)(Stain *et al.* 2016) which found three

transitions in the CBT group but none in the control group, and the other was the as-yet unpublished PREVENT trial (Bechdolf *et al.*, 2011) which randomized 216 individuals to CBT, antipsychotic treatment or standard clinical management (plus placebo) A preliminary report of this study (Bechdolf *et al.*, 2017) found a smaller number of transitions in the CBT group compared to clinical management (19.2 % vs 30.0 %), but the difference did not reach statistical significance(Bechdolf *et al.* 2017).

Conclusions

CBT was originally introduced to treat the positive symptoms of schizophrenia, but its effect on these, according to convergent meta-analytic evidence, is small. A stronger effect on hallucinations remains a possibility, but this has to be treated with caution given that it is based on a meta-analysis of a relatively small number of studies (van der Gaag *et al.* 2014b, p.), and a subsequent large trial found no effect on voice frequency and distress (Birchwood *et al.*, 2014)(Birchwood *et al.* 2014). A considerable body of trials now makes it clear that CBT is ineffective against negative symptoms, either in generic or specially adapted forms. CBT, on present evidence, does not prevent relapse.

Where CBT may hold more promise is in areas of symptomatology not specifically targeted by antipsychotic drugs. Relatively large effects have been reported in large, well-conducted trials for worry related to delusions and harmful compliance with auditory hallucinations. The meta-analytic database on such symptoms, however, is small and not particularly encouraging as it stands.

The question of whether CBT is useful in preventing transition to psychosis in high-risk individuals currently hangs in the balance. The disagreement between the meta-analysis

of Hutton and Taylor (2014) and the network meta-analysis of Davies *et al.* (2018) is clearly due to methodological factors, specifically study inclusion. The equivocal findings of the PREVENT trial – of a relatively substantial but statistically non-significant reduction in transition rate – will require integration into further meta-analyses for interpretation, and even then the conclusion may not be decisive.

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