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# Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic drugs: a single-blind randomised controlled trial



Anthony P Morrison, Douglas Turkington, Melissa Pyle, Helen Spencer, Alison Brabban, Graham Dunn, Tom Christodoulides, Rob Dudley, Nicola Chapman, Pauline Callcott, Tim Grace, Victoria Lumley, Laura Drage, Sarah Tully, Kerry Irving, Anna Cummings, Rory Byrne, Linda M Davies, Paul Hutton

## Summary

**Background** Antipsychotic drugs are usually the first line of treatment for schizophrenia; however, many patients refuse or discontinue their pharmacological treatment. We aimed to establish whether cognitive therapy was effective in reducing psychiatric symptoms in people with schizophrenia spectrum disorders who had chosen not to take antipsychotic drugs.

**Methods** We did a single-blind randomised controlled trial at two UK centres between Feb 15, 2010, and May 30, 2013. Participants aged 16–65 years with schizophrenia spectrum disorders, who had chosen not to take antipsychotic drugs for psychosis, were randomly assigned (1:1), by a computerised system with permuted block sizes of four or six, to receive cognitive therapy plus treatment as usual, or treatment as usual alone. Randomisation was stratified by study site. Outcome assessors were masked to group allocation. Our primary outcome was total score on the positive and negative syndrome scale (PANSS), which we assessed at baseline, and at months 3, 6, 9, 12, 15, and 18. Analysis was by intention to treat, with an ANCOVA model adjusted for site, age, sex, and baseline symptoms. This study is registered as an International Standard Randomised Controlled Trial, number 29607432.

**Findings** 74 individuals were randomly assigned to receive either cognitive therapy plus treatment as usual (n=37), or treatment as usual alone (n=37). Mean PANSS total scores were consistently lower in the cognitive therapy group than in the treatment as usual group, with an estimated between-group effect size of  $-6.52$  (95% CI  $-10.79$  to  $-2.25$ ;  $p=0.003$ ). We recorded eight serious adverse events: two in patients in the cognitive therapy group (one attempted overdose and one patient presenting risk to others, both after therapy), and six in those in the treatment as usual group (two deaths, both of which were deemed unrelated to trial participation or mental health; three compulsory admissions to hospital for treatment under the mental health act; and one attempted overdose).

**Interpretation** Cognitive therapy significantly reduced psychiatric symptoms and seems to be a safe and acceptable alternative for people with schizophrenia spectrum disorders who have chosen not to take antipsychotic drugs. Evidence-based treatments should be available to these individuals. A larger, definitive trial is needed.

**Funding** National Institute for Health Research.

## Introduction

Antipsychotic drugs are usually the first line of treatment for schizophrenia, and clinical guidelines report clear benefits in terms of symptom reduction.<sup>1</sup> Furthermore, findings have shown that antipsychotic use is associated with decreased mortality overall,<sup>2</sup> perhaps because of a protective effect against suicide,<sup>2</sup> and with significant benefits for relapse prevention.<sup>3</sup> However, evidence also shows that many patients choose to refuse or discontinue their pharmacological treatment. The largest trial<sup>4</sup> to compare atypical antipsychotics found that 74% of patients with schizophrenia discontinued their drugs over 18 months, and rates of drug non-compliance in patients with schizophrenia can be as high as 40–50%.<sup>5</sup> Patients with psychosis are often ambivalent about taking drugs,<sup>6</sup> and evidence suggests that the effectiveness of such drugs has been overestimated, whereas the severity of their adverse effects have been underestimated.<sup>7</sup> A

systematic review concluded that the improvements claimed for antipsychotics are of questionable clinical relevance,<sup>8</sup> and a multiple-treatments meta-analysis<sup>9</sup> showed that although differences in efficacy between antipsychotics and placebo were noted, they were smaller than those for most of the analysed adverse effects.<sup>10</sup> Research suggests that adverse effects include structural abnormalities in brain volume,<sup>11</sup> increased risk of sudden cardiac death,<sup>12</sup> and substantial weight gain induced by antipsychotics,<sup>13</sup> which is associated with cardiovascular and metabolic risks.

Given the cost-benefit profile, some choices to refuse antipsychotics might suggest a rational decision rather than an irrational consequence of psychosis. Many people admitted to hospital with psychosis retain the capacity to make decisions about treatment,<sup>14</sup> and a review of choice and decision making in people using mental health services concluded that service users want

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School of Psychological Sciences  
(Prof A P Morrison D Clin Psy, M Pyle BSc, N Chapman D Clin Psy, S Tully MSc, P Hutton D Clin Psy) and Centre for Biostatistics (Prof G Dunn PhD) and Centre for Health Economics, Institute of Population Health (Prof L M Davies MSc), University of Manchester, Manchester, UK; Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK (Prof A P Morrison, M Pyle, N Chapman, L Drage MPhil, S Tully, K Irving BSc, R Byrne BSc, P Hutton); Newcastle University,

Newcastle-upon-Tyne, UK (Prof D Turkington MD, H Spencer BA, R Dudley PhD, A Cummings BSc); Northumberland, Tyne and Wear NHS Mental Health Foundation Trust, Newcastle-upon-Tyne, UK (Prof D Turkington, H Spencer, T Christodoulides D Clin Psy, R Dudley, P Callcott MSc, A Cummings); University of Durham, Durham, UK (A Brabban D Clin Psy); and Tees, Esk, and Wear Valley NHS Mental Health Foundation Trust, County Durham, UK (A Brabban, T Grace PG Dip, V Lumley PG Dip)

Correspondence to: Prof Anthony P Morrison, School of Psychological Sciences, University of Manchester, Manchester M13 9PL, UK [tony.morrison@manchester.ac.uk](mailto:tony.morrison@manchester.ac.uk)

to be offered more than just drugs.<sup>15</sup> Cognitive therapy has proven to be effective when delivered in combination with antipsychotic drugs, with findings from several meta-analyses showing robust support for this approach.<sup>16</sup> Our exploratory single-group study assessed cognitive therapy in 20 participants with schizophrenia spectrum disorders who had not been taking antipsychotic drugs for at least 6 months.<sup>17</sup> We noted significant beneficial effects on primary and secondary outcomes at the end of treatment and follow-up, and good acceptability, and no patients significantly deteriorated. However, such a trial clearly suggests the possibility of bias resulting from allegiance effects and non-masked ratings; the absence of randomisation to a control group was also problematic. These methodological limitations probably resulted in inflated estimates of treatment effects because cognitive therapy for psychosis trials that attempt masking are associated with a reduction of effect sizes of nearly 60%.<sup>16</sup>

In this study, we aimed to assess the feasibility and effectiveness of cognitive therapy for people with schizophrenia spectrum disorders who had decided not to take antipsychotic drugs.

## Methods

### Study design and participants

We did this single-blind, randomised, controlled, pilot trial between Feb 15, 2010, and May 30, 2013, at two UK centres in Manchester and Newcastle.

Eligible participants aged 16–65 years were in contact with mental health services, and either met International Classification of Diseases–tenth revision (ICD-10) criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met entry criteria for an early intervention for psychosis service (operationally defined with the Positive and Negative Syndrome Scale [PANSS]) to allow for diagnostic uncertainty in early phases of psychosis and the fact that most early-episode cases in the UK will receive their services from such specialist teams, consistent with NICE guidelines. Participants had also had either at least 6 months without antipsychotic drugs and continuing symptoms or had never received antipsychotics and had chosen not to; all participants scored at least 4 on PANSS delusions or hallucinations, or at least 5 on suspiciousness or persecution, conceptual disorganisation, or grandiosity. All participants were identified via care coordinators and relevant mental health staff within participating mental health trusts at the two study sites. Exclusion criteria were present receipt of antipsychotic drugs; moderate to severe learning disability; organic impairment; participants not having the capacity to consent to research participation; non-English-speaking participants (because their inclusion would prevent the use of standardised assessment techniques); acute inpatient care settings; receipt of cognitive therapy for psychosis or previous cognitive therapy for other disorders in the past 2 years; and a primary diagnosis of substance or alcohol abuse.

Diagnosis was established with case notes and the ICD-10 checklist. A consultant psychiatrist (DT) confirmed all diagnoses, with application of ICD-10 to vignettes based on the PANSS assessments for all cases, including those in early intervention services who did not have a formal diagnosis in their medical records. Further details about our ascertainment strategy, referral sources, reasons for choosing not to take antipsychotics, and additional participant characteristics are provided elsewhere.<sup>18</sup> Our protocol was approved by the National Research Ethics Service of the UK's National Health Service (reference 09/H1014/53). All participants provided written informed consent.

After original ethical approval of the trial in October 2009, several amendments to the protocol were made: addition of secondary measures including the CHOICE and EQ-5D; addition of some secondary measures for an add-on hypothesis about childhood trauma at month 3; removal of some secondary measures at months 3, 6, and 15 to reduce participant burden; the ability to retain people if they lose capacity, which was an event that did not actually take place throughout the trial; and a minor change to the exclusion criteria to signify the population and increase generalisability (allowing inclusion of those with substance dependence as long as it was not the primary diagnosis).

### Randomisation and masking

Participants were randomly assigned electronically (1:1) by a computerised system (Open Clinical Data Management System [OpenCDMS], version 1.7.4)<sup>19</sup> with permuted block sizes of four or six, to receive cognitive therapy plus treatment as usual, or treatment as usual alone. Because of the variability of treatment as usual, and because this control is dependent on local service configurations and specific sources of referral to the trial, randomisation was first stratified by study site. OpenCDMS then sent out email notifications of the allocation to the therapists and trial manager. Thus, assessors were masked to group allocation and randomisation was independent. We used many strategies to achieve masked ratings: research workers were not involved in the randomisation process; therapists were required to consider room use and diary arrangements in view of potential blind breaks; and patients were reminded by assessors not to talk about treatment allocation. 13 blind breaks (representing 18% of participants) were reported by research assistants with a standard form: four (31%) of these breaks were with treatment as usual and nine (69%) with cognitive therapy. In cases where concealment was broken, another rater assessed the patient for all subsequent assessments or the ratings were discussed with a masked rater and consensus reached. This assessment strategy ensured that only a minority of a total of about 500 assessments had their validity threatened by absence of rater masking.

## Procedures

In addition to treatment as usual, participants allocated to the therapy group received cognitive therapy on the basis of a specific cognitive model.<sup>20</sup> 26 sessions were offered on a roughly weekly basis for a maximum of 9 months, plus up to four booster sessions in the subsequent 9 months. Cognitive therapy requires an individualised, problem-oriented approach and incorporates a manualised process of assessment and formulation. The central features of our approach to treatment of psychosis involve normalisation and evaluation of the appraisals that people make, helping them to test such appraisals with use of behavioural experiments, and helping them to identify and modify unhelpful cognitive and behavioural responses. A more detailed analysis of the treatment strategies can be found in our treatment manuals.<sup>21,22</sup> Fidelity to the treatment protocol was ensured by regular supervision of the therapists and was assessed by rating of recordings of sessions with a version of the Cognitive Therapy Scale-Revised<sup>23</sup> (CTS-R), and by review of written, structured session records that were completed by the therapist after each session. Therapy supervision was provided by means of regular meetings between therapists and the chief investigator. Ten sessions were rated on the CTS-R, and all were rated as competent or above.

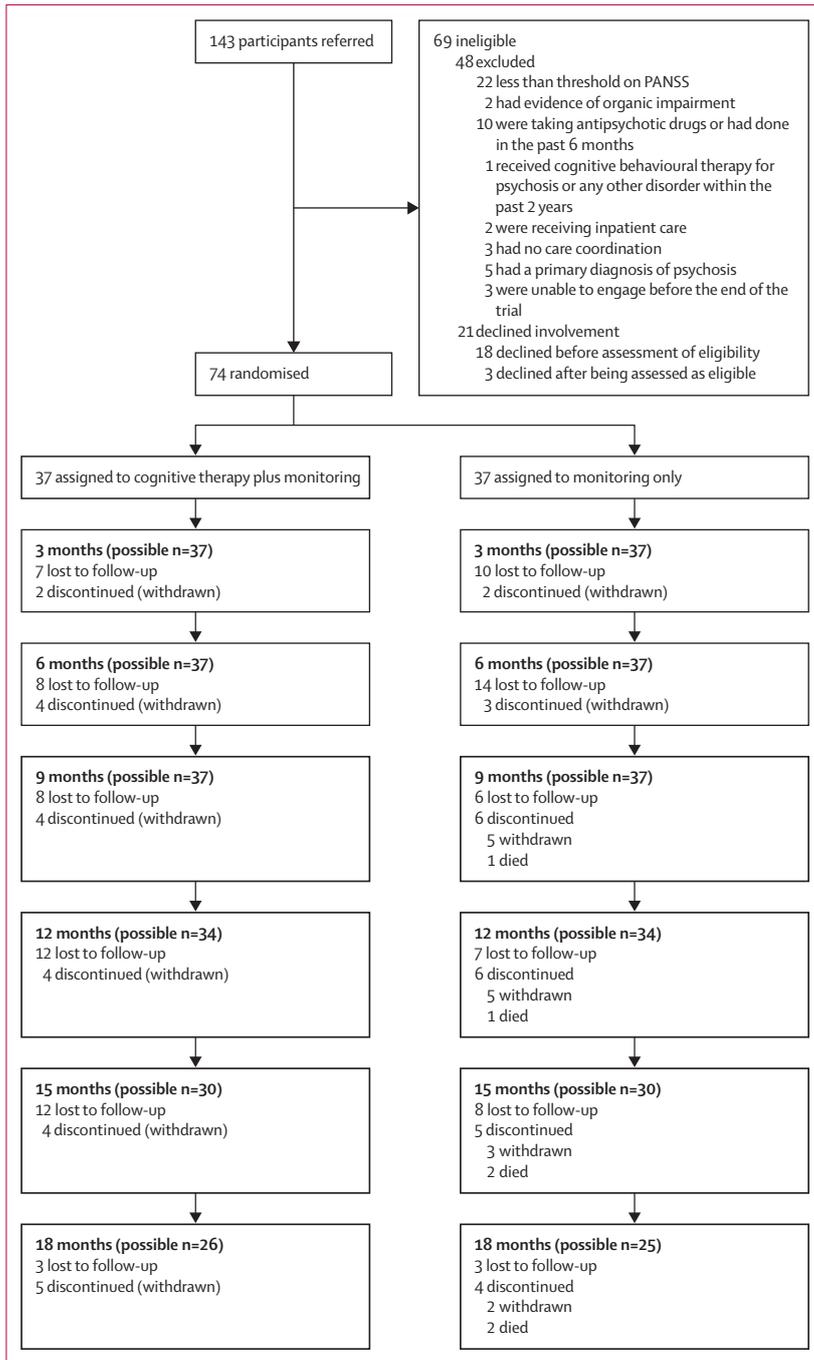
Eight therapists (two at the Manchester sites and six in Newcastle) contributed to the delivery of cognitive therapy. The number of participants treated by each therapist ranged between two and 18 (mean 4.6, SD 5.5). Five therapists were clinical psychologists (doctoral level), two were nurses with an additional specialist qualification in cognitive therapy, and one was a consultant psychiatrist with specialist training in cognitive therapy. All therapists received additional training associated with the trial manual, and regular supervision.

All participants received treatment as usual plus regular monitoring (incorporating a PANSS assessment from a research assistant), which provided benefits over routine care because it aimed to provide warm, empathic, and non-judgmental face-to-face contact, supportive listening, signposting to appropriate local services for unmet needs, and crisis management when needed (usually by referral to a local crisis team, early intervention service, or psychiatric liaison within emergency departments). Treatment as usual was variable across both sites, although both were chosen partly because they had comprehensive early intervention services. In practice, participants within these services received regular care-coordination and psychosocial interventions, including the offer of family interventions, whereas individuals from other community-based services often received little more than irregular contact with care coordinators, and many of these participants were discharged by their clinical teams during the trial for non-attendance or continued reluctance to accept medicine.

## Outcomes

Our primary outcome was total score on the PANSS,<sup>24</sup> which we assessed at baseline, and at months 3, 6, 9, 12, 15, and 18. The PANSS is a clinician-administered, thirty-item, semi-structured interview consisting of seven items assessing positive symptomatology (eg, hallucinations, delusions, conceptual disorganisation); seven items assessing negative symptomatology (eg, blunted affect, passive or apathetic social avoidance); and 16 items assessing general psychopathology (eg, depression, anxiety, poor insight, guilt). All items are scored between 1 (not present) and 7 (severe). Several studies have shown the reliability and validity of the PANSS.<sup>25</sup> We assessed inter-rater reliability regularly (on nine occasions) throughout the trial, with both video and role-play assessments with all trial raters ( $n=5$ ) participating; intra-class correlation coefficients indicated good reliability between raters (mean 0.83, SD 0.12).

Secondary outcomes included dimensions of psychotic experiences such as severity, distress and disability, measured with the Psychotic Symptom Rating Scales;<sup>26</sup> a clinician-administered, semi-structured interview consisting of 11 items assessing dimensions of auditory hallucinations, and six items assessing dimensions of delusional beliefs. All items are scored from 0 to 4, with higher scores showing more severe phenomena. Factor analyses show that the delusions scale has two subscales (emotional and cognitive) and the hallucinations scale has three subscales (emotional, physical, and cognitive).<sup>26</sup> We also included a user-defined measure of recovery (QPR<sup>27</sup>), which is a questionnaire developed collaboratively with service users that measures subjective recovery. We used a 15-item version of the questionnaire, which is more reliable than the original 22-item version ( $\alpha$  0.91). Participants rated their agreement with statements on a 5-point Likert scale, from strongly disagree to strongly agree. We assessed social functioning with the Personal and Social Performance Scale;<sup>28</sup> a 100-point, single-item rating scale based on an interview that assesses patient's functioning in four areas (socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviour). We assessed emotional distress with the Beck Depression Inventory for Primary Care (BDI-PC)<sup>29</sup> and the Social Interactions Anxiety Scale (SIAS).<sup>30</sup> The SIAS has a recommended cutoff of greater than 36, showing a probable diagnosis of social anxiety disorder, and the BDI-PC has a recommended cutoff of greater than 3, showing a probable diagnosis of major depressive disorder. We recorded prescriptions of antipsychotic and other psychiatric drugs. Most assessments were done in the participant's home. Several other measures were administered (such as EQ-5D, the CHOICE, the Metacognitions Questionnaire, and the Personal Beliefs about Experiences Questionnaire), but these were intended for secondary analyses, such as predictors of outcome and cost effectiveness. We report on all



**Figure: Trial profile**  
Possible numbers of participants refers to the maximum possible at this timepoint on the basis of variable length of follow-up time.

outcomes that were specified in our published protocol and analysis plan.<sup>18</sup>

After randomisation, all participants received monitoring assessments every 3 months up to a total of 18 months. Our variable follow-up period meant that participants recruited in the first 18 months of the study (from February, 2010, to August, 2011) were planned to receive the full 18 months of

	CT plus TAU (n=37)	TAU only (n=37)
Age (years)	32.95 (13.11)	29.68 (11.95)
Sex		
Male	17 (46%)	22 (59%)
Female	20 (54%)	15 (41%)
PANSS total	70.24 (13.75)	73.27 (13.42)
PANSS positive	20.30 (5.22)	21.65 (4.47)
PANSS negative	13.54 (3.17)	15.49 (5.26)
PANSS general	36.41 (7.94)	36.14 (7.05)
PSYRATS unusual beliefs (cognitive)	10.11 (4.18)	10.43 (2.91)
PSYRATS unusual beliefs (emotional)	5.17 (2.69)	5.00 (2.51)
PSYRATS voices (cognitive)	5.28 (5.13)	7.73 (5.23)
PSYRATS voices (emotional)	5.86 (6.43)	7.92 (5.93)
PSYRATS voices (physical)	5.62 (5.40)	7.37 (5.10)
PSP	56.84 (16.45)	50.03 (16.19)
QPR total	29.35 (11.15)	28.76 (11.78)
BDI-PC total	10.54 (5.21)	9.41 (4.03)
SIAS total	40.43 (19.76)	45.15 (15.19)
PANSS G12 (insight)	3.03 (1.67)	3.20 (1.67)
PANSS insight >3 (moderate or higher problems)	17 (46%)	17 (46%)

Data are mean (SD) or n (%), unless otherwise indicated. CT=cognitive therapy. TAU=treatment as usual. PANSS=positive and negative syndrome scale. PSYRATS=psychotic symptom rating scales. PSP=personal and social performance. QPR= questionnaire on the process of recovery. BDI-PC=Beck depression inventory for primary care. SIAS=social interaction anxiety scale.

**Table 1: Baseline characteristics**

follow-up. Participants recruited thereafter were offered steadily reducing follow-up periods dependent on time of recruitment (this approach was used to maximise value for money, with a view to obtain as much data as possible for participants recruited in early phases of the trial, with shorter follow-up periods for those recruited in later phases). The minimum follow-up period was 9 months; follow-ups at 12, 15, and 18 months had fewer participants because those most recently recruited could not be followed up at these timepoints within the funded resources.

**Statistical analysis**

With 30 participants per group, with a *t* test at a two-tailed significance of 0.05, we had over 80% power to detect an effect size of 0.8; if the significance level were changed to 15%, which might be appropriate for a pilot study, 30 participants per group would provide 80% power to detect an effect size of 0.6. We chose a recruitment target of 80 (40 per site) allowing for a dropout rate of up to 25%.

Statistical analysis was agreed with the data monitoring and ethics committee, and the a-priori analysis plan was published.<sup>18</sup> Analyses were undertaken in STATA (version 12). Primary analysis was by intention to treat. Changes in all primary and secondary outcomes were analysed with STATA's xtreg command to fit random-effects regression models (essentially, repeated measures ANCOVAs) with summed scores as dependent variables,

	3 months		6 months		9 months		12 months		15 months		18 months	
	CT (n=37)	TAU (n=37)	CT (n=37)	TAU (n=37)	CT (n=37)	TAU (n=37)	CT (n=34)	TAU (n=34)	CT (n=30)	TAU (n=30)	CT (n=26)	TAU (n=25)
PANSS total	62.93 (13.72); n=28	72.88 (15.56); n=24	59.96 (14.47); n=23	66.95 (11.70); n=19	57.95 (14.99); n=22	63.26 (13.21); n=23	58.56 (18.85); n=18	68.33 (15.03); n=21	54.68 (14.61); n=19	69.94 (14.35); n=16	56.47 (18.22); n=17	71.24 (20.35); n=17
PANSS positive	18.14 (5.34); n=28	21.71 (5.83); n=24	17.04 (5.36); n=23	18.32 (4.40); n=19	16.00 (5.94); n=22	17.00 (4.85); n=23	16.32 (7.94); n=19	18.62 (5.26); n=21	14.05 (5.36); n=19	19.44 (5.75); n=16	14.63 (6.18); n=19	18.83 (7.26); n=18
PANSS negative	13.00 (3.16); n=28	14.88 (5.77); n=24	12.48 (3.63); n=23	13.95 (3.76); n=19	12.5 (3.38); n=22	14.26 (4.21); n=23	12.61 (4.24); n=18	15.95 (5.89); n=21	12.05 (3.85); n=19	16.19 (5.49); n=16	12.53 (2.83); n=17	16.59 (6.65); n=17
PANSS general	31.79 (7.89); n=28	36.29 (8.26); n=24	30.43 (8.63); n=23	34.68 (7.17); n=19	29.45 (7.68); n=22	32.00 (6.98); n=23	29.78 (7.95); n=18	33.76 (7.80); n=21	28.58 (7.71); n=19	34.31 (7.10); n=16	29.22 (10.51); n=18	35.82 (9.74); n=17
QPR total	33.91 (11.36); n=23	29.34 (12.64); n=21	31.52 (15.12); n=21	30.42 (10.99); n=19	35.12 (11.76); n=25	32.10 (8.80); n=21	34.00 (16.41); n=16	31.87 (9.64); n=15	41.63 (11.22); n=16	29.69 (9.71); n=13	39.50 (15.46); n=16	29.38 (8.76); n=16
PSP	59.81 (16.55); n=27	49.70 (14.46); n=24	59.74 (17.88); n=23	51.89 (16.09); n=19	65.00 (12.75); n=23	56.74 (15.02); n=23	65.37 (17.63); n=19	52.95 (15.50); n=21	65.84 (18.22); n=19	53.53 (18.75); n=15	64.74 (20.24); n=19	55.94 (20.29); n=18
BDI	7.83 (5.58); n=24	9.65 (4.69); n=23	7.57 (5.89); n=21	7.37 (3.61); n=19	6.35 (5.93); n=26	7.14 (3.35); n=21	7.44 (6.34); n=18	7.00 (3.54); n=17	4.50 (4.05); n=16	7.38 (4.29); n=13	5.50 (5.63); n=16	7.38 (5.16); n=16
SIAS	35.18 (18.75); n=22	44.53 (13.21); n=19	37.63 (18.40); n=19	40.78 (12.88); n=18	31.71 (16.34); n=24	40.48 (13.88); n=21	30.00 (22.38); n=15	41.86 (14.87); n=14	28.59 (18.21); n=17	45.27 (16.44); n=11	31.31 (20.87); n=16	44.06 (18.21); n=16
PSYRATS delusions (cognitive)	7.82 (4.97); n=27	9.57 (3.75); n=23	7.78 (4.88); n=23	8.00 (3.41); n=18	6.63 (5.32); n=24	7.28 (4.99); n=25	6.00 (5.75); n=19	8.63 (4.21); n=19	3.47 (4.66); n=19	8.81 (4.36); n=16	5.32 (5.39); n=19	7.18 (4.76); n=17
PSYRATS delusions (emotional)	3.85 (3.21); n=27	4.78 (2.88); n=23	3.61 (3.24); n=23	3.28 (3.14); n=18	3.21 (3.36); n=24	2.92 (2.75); n=25	3.05 (3.37); n=19	4.11 (2.94); n=19	1.26 (2.51); n=19	3.38 (2.68); n=16	2.21 (2.72); n=19	3.47 (2.63); n=17
PSYRATS voices (cognitive)	3.52 (4.78); n=27	6.78 (5.78); n=23	2.26 (3.89); n=23	6.00 (5.45); n=19	2.73 (4.46); n=26	4.82 (5.29); n=27	3.25 (3.70); n=20	5.37 (5.92); n=19	2.42 (3.88); n=19	5.94 (5.13); n=17	0.79 (2.37); n=19	5.65 (5.36); n=17
PSYRATS voices (emotional)	3.41 (5.40); n=27	5.96 (6.09); n=23	2.35 (4.25); n=23	4.26 (5.95); n=19	2.81 (5.02); n=26	5.07 (5.90); n=27	3.74 (5.53); n=19	4.26 (6.04); n=19	2.00 (3.84); n=19	5.12 (6.12); n=17	0.50 (2.12); n=18	6.00 (6.49); n=18
PSYRATS voices (physical)	4.37 (5.49); n=27	7.04 (5.92); n=23	3.00 (4.84); n=23	5.37 (5.20); n=19	3.31 (4.76); n=26	4.82 (5.41); n=27	4.35 (4.67); n=20	5.76 (5.93); n=21	2.58 (4.02); n=19	5.94 (4.89); n=17	1.11 (3.32); n=19	6.83 (6.21); n=18

Data are mean (SD), unless otherwise indicated. CT=cognitive therapy. TAU=treatment as usual. PANSS=positive and negative syndrome scale. QPR=questionnaire on the process of recovery. PSP=personal and social performance. BDI=Beck depression inventory. SIAS=social interaction anxiety scale. PSYRATS=psychotic symptom rating scales.

**Table 2: Primary and secondary outcome variables at months 3, 6, 9, 12, 15, and 18**

allowing for attrition and the variable follow-up times introduced by the trial design. Covariates included site, sex, age, and the baseline value of the relevant outcome measure. Use of these models allowed for analysis of all available data, in the assumption that data were missing at random,<sup>31</sup> conditional on adjustment for centre, age, sex, and baseline scores. The missing-at-random assumption seems to be the most realistic, in view of the planned variation in maximum follow-up times and the many other factors likely to affect drop-out; additionally, the assumption is routinely used in analyses of data from longitudinal trials. We report numbers of participants in each group (completer-only data ie, observed cases) achieving improvement or deterioration in adjusted PANSS total scores,<sup>32</sup> as has been recommended for trials using the PANSS.<sup>33</sup> We report estimated treatment effects,

with their standard errors, significance levels, and 95% CIs. All treatment effects reported here are estimates of the effects common to all follow-up times.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or in the decision to submit for publication. The corresponding author and GD had full access to all the data in the study and had the final decision to submit for publication.

### Results

The figure shows the trial profile. 74 individuals were randomised to the cognitive therapy plus treatment as usual group (n=37), or the treatment as usual alone group

	Estimate (SE)*	95% CI	p value
PANSS total	-6.52 (2.18)	-10.79 to -2.25	0.003
PANSS positive	-2.22 (0.91)	-4.00 to -0.44	0.015
PANSS negative	-1.02 (0.67)	-2.35 to 0.30	0.13
PANSS general	-3.63 (1.21)	-5.99 to -1.27	0.003
Secondary outcomes			
PSYRATS unusual beliefs cognitive	-2.08 (0.82)	-3.69 to -0.47	0.011
PSYRATS unusual beliefs emotion	-0.70 (0.51)	-1.71 to 0.30	0.17
PSYRATS voices cognitive	-2.1 (0.95)	-3.96 to -0.23	0.028
PSYRATS voices emotion	-1.44 (1.06)	-3.52 to 0.64	0.174
PSYRATS voices physical	-1.76 (0.89)	-3.51 to -0.02	0.048
QPR*	3.32 (1.9)	-0.39 to 7.04	0.08
PSP*	5.47 (2.7)	0.18 to 10.77	0.043
BDI	-0.73 (0.79)	-2.29 to 0.83	0.357
SIAS	-1.63 (3.17)	-7.84 to 4.58	0.607

PANSS=positive and negative syndrome scale. PSYRATS=psychotic symptom rating scales. QPR=questionnaire on the process of recovery. PSP=personal and social performance. BDI=Beck depression inventory. SIAS=social interaction anxiety scale. \*Negative estimates show that, on average, scores for the cognitive therapy group were lower than those for the treatment as usual group, except for QPR and PSP, for which a higher score is preferable.

**Table 3: Estimates of treatment effect (common to all follow-up times)**

(n=37). We stopped before the target of 80 individuals in accordance with our recruitment timeline, on the basis of restricted resources, to ensure that we had the possibility to obtain 9 month data for all participants. Baseline characteristics were similar between groups (table 1).

Recruitment was fairly successful: we recruited over target in one of the two sites, and had a final sample that was 93% of target (figure). Our referral to randomised ratio was 2:1, and only three (2%) of 143 referrals declined participation after being assessed as eligible, suggesting good willingness to be randomised, and to consider cognitive therapy, within this population (figure). Participants allocated to cognitive therapy received a mean of 13.3 sessions (SD 7.57; range 2–26), with each session lasting roughly 1 h (these figures do not include the four booster sessions that were available). Adherence to cognitive therapy was reasonably good, with no patients not attending any sessions, and 30 (82%) having at least six or more sessions. Retention within the trial was reasonable, with few discontinuations and withdrawals in each group (figure), and missing data rates of 29.7% at primary endpoint and 29.4% at follow-up. 68 (92%) of participants had a diagnosis of schizophrenia, two (3%) were schizoaffective, three (4%) had persistent delusional disorder, and one (1%) had psychosis not otherwise specified.

For the primary outcome of PANSS total scores, mean scores were consistently less in the cognitive therapy group than in the treatment as usual group (table 2)—low PANSS scores are preferable. This finding is shown in the estimates of treatment effect (table 3), with the estimated between-group effect size (unstandardised) for the PANSS total score equating to a standardised effect size (Cohen's *d*) of 0.46. The effects on the positive and

general subscales are consistent with this finding, but cognitive therapy seemed to have little or no effect on negative symptoms (table 2). On the basis of the PANSS data, we noted, on average, no overall deterioration in either group (table 2).

For the secondary outcomes, the estimated treatment effects for the PSYRATS scores in table 3 are consistent with the findings for the primary outcome, but not all are statistically significant. For the other outcomes, we recorded a significant effect in favour of cognitive therapy for social functioning (personal and social performance scale), but no differences on our measures of recovery (questionnaire on the process of recovery), depression (Beck depression inventory), or anxiety (social interaction anxiety scale; table 3). For no outcome did treatment effects vary with time of follow-up (we noted no significant treatment by time interactions).

By examination of the proportion of participants achieving good clinical outcomes in each disorder (defined by use of an improvement of >50% in adjusted PANSS total scores), we noted that, at 9 months, seven (32%) of 22 participants in the cognitive therapy group, and three (13%) of 23 from the treatment as usual group had achieved good clinical outcomes (table 4). At 18 months seven (41%) of 17 receiving cognitive therapy and three (18%) of 17 receiving treatment as usual had achieved good clinical outcomes (table 4). Two participants in each group had significant deterioration (defined by use of a deterioration of >50% in adjusted PANSS total scores; table 5). We recorded eight serious adverse events, two of which were in patients in the cognitive therapy group (both of which happened after therapy; one attempted overdose, one presenting risk to others) and six were in those in the treatment as usual group (two deaths, both of which were deemed unrelated to trial participation or mental health; three compulsory admissions to hospital for treatment under the mental health act and one attempted overdose). Table 5 shows data for type, number, and length of stay for voluntary hospital admissions. We recorded only one voluntary hospital admission in the follow-up phase, in a patient in the cognitive therapy group, which was voluntary and lasted 4 days. All serious adverse events and hospital admissions were in separate participants.

With regards to use of antipsychotic drugs throughout the lifetime of the trial, ten (4%) of 37 participants in the cognitive therapy group were prescribed antipsychotics after randomisation (eight during the treatment window and two during the follow-up phase) as were ten (4%) of 37 in the treatment as usual group (nine during the treatment window and one during the follow-up phase). To explore the potential contribution that drugs might have had in individual participants, we assessed the extent of change in PANSS scores for those who commenced antipsychotics by 9 months and 18 months (table 4). Of patients in the cognitive therapy group prescribed antipsychotics in the treatment phase, one

	N	Increase (deterioration)					0% change	Reduction (improvement)			
		100%	75-100%	50-74%	25-49%	0-24%		0-24%	25-49%	50-74%	75-100%
CT (9 months)	22	1 (5%)*	0	0	1 (5%)*	3 (14%)	2 (9%)*	3 (14%)*	5 (23%)†	4 (18%)	3 (14%)†
TAU (9 months)	23	0	0	0	2 (9%)	2 (9%)*	2 (9%)*	9 (39%)‡	5 (22%)†	2 (9%)	1 (4%)
CT (18 months)	17	0	0	1 (6%)	1 (6%)	0	0	4 (24%)†	4 (24%)	6 (35%)†	1 (6%)
TAU (18 months)	17	0	0	2 (12%)	2 (12%)†	3 (18%)*	1 (6%)	4 (24%)†	2 (12%)	2 (12%)*	1 (6%)

Data are n (%), unless otherwise indicated. CT=cognitive therapy, TAU=treatment as usual. \*One participant commenced antipsychotic drugs, of the total number within each change category. †Two participants commenced antipsychotic drugs, of the total number within each change category. ‡Three participants commenced antipsychotic drugs, of the total number within each change category.

**Table 4: Number of participants achieving improvement/deterioration on adjusted PANSS total scores at 9 and 18 months**

individual was also prescribed antidepressants, and of those in the treatment as usual group prescribed antipsychotics in the treatment phase, five were also prescribed antidepressants. Additionally, nine participants in the cognitive therapy group were taking antidepressants in the treatment phase (with no new cases in follow-up), as were eight participants in the treatment as usual group (with 2 new cases in follow-up).

## Discussion

To our knowledge, this study is the first randomised trial of cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic drugs. Our findings show that cognitive therapy significantly reduced the severity of psychiatric symptoms in this population. Additionally, cognitive therapy significantly improved personal and social functioning and some dimensions of delusional beliefs (cognitive) and voice hearing (cognitive and physical). Therapy did not significantly affect the amount of distress associated with delusional beliefs or voice hearing, or levels of depression, social anxiety, and self-rated recovery.

On average, neither group deteriorated over time, in a population that has been assumed to deteriorate without total adherence to drugs;<sup>34</sup> in fact, some participants receiving treatment as usual who were not taking drugs achieved good clinical outcomes, and more did with the addition of cognitive therapy. However, some individual patients not taking drugs did have deterioration and adverse events, and this finding was noted on both groups (additionally we might have missed some such events, in view of high rates of missing data and non-engagement with services). We also showed that cognitive therapy is an acceptable intervention for a population who are usually considered to be very challenging to engage by mental health services, with low rates of drop out and withdrawal, and very few referrals refusing randomisation after assessment as eligible.

These results are consistent with findings from clinical trials of cognitive therapy for psychosis to date. Most trials have shown that severity of psychiatric symptoms can be reduced over a moderate timeframe in people taking antipsychotic drugs, with an average effect size of 0.4.<sup>16</sup> Our study found a similar effect size

	CT plus TAU (n=37)		TAU (n=37)	
	Participants admitted	Length of stay (days)	Participants admitted	Length of stay (days)
Voluntary admission	4 (11%)	12.25 (9.54)	1 (3%)	27.00 (0.00)
Compulsory admission	0	..	3 (8%)	42.00 (22.65)

Data are n (%) or mean (SD). CT=cognitive therapy, TAU=treatment as usual.

**Table 5: Hospital admissions during the treatment phase**

in people who had chosen not to take such drugs. Although this effect size is small to moderate, the size on psychiatric symptoms in our study is similar to the median effect size reported for overall symptoms in a large meta-analysis of 15 antipsychotic drugs versus placebo (median 0.44).<sup>9</sup> The baseline PANSS total scores for our trial are notably higher than for most trials of cognitive therapy for psychosis, suggesting that our results might be reasonably generalisable and are not attributable to participants being relatively well at study entry (our sample would correspond to a moderately ill population according to thresholds for the PANSS<sup>35</sup>). Indeed, many participants were regarded as challenging to engage by their clinical teams, with some being discharged as a result, and our therapists frequently had to work hard to engage them and identify a shared goal. Cognitive therapy seemed to be acceptable to this population. Because equal numbers of participants in each group started drugs, the effects noted are not likely to be due to drugs, especially because more participants in the treatment as usual group started antipsychotics during the initial treatment window. Examination of the improvement or deterioration in individuals who started drugs also suggests that the benefits are not likely to be attributable to antipsychotics.

Our trial shows methodological rigour in several ways. Importantly, we pre-specified our primary and secondary outcomes, thus reducing the likelihood of type 1 errors. Furthermore, use of more than one site should increase generalisability to routine clinical service provision. However, our trial has some methodological difficulties.

**Panel: Research in context****Systematic review**

Although findings from systematic reviews and meta-analyses<sup>1,16,36</sup> show that robust evidence exists of the effectiveness of cognitive therapy for psychosis in addition to antipsychotics compared with treatment as usual, no randomised controlled trials have been done of cognitive therapy in people with psychotic disorders not taking antipsychotics. We searched the reference lists of the reviews mentioned above and a Cochrane review;<sup>37</sup> furthermore, we searched CENTRAL, PubMed, and Current Controlled Trials. We limited the search to 2009–13, because the last search for the reviews was done in 2010. We searched titles and abstracts for “cognitive behavioural therapy”, “cognitive therapy”, “psychosis”, “schizophrenia” and “trial”, and limited our search to reports published in English.

**Interpretation**

Our findings suggest that cognitive therapy is an acceptable, safe, and effective treatment alternative for people who choose not to take antipsychotics. Evidence-based treatments should be available to these people. A larger definitive trial is needed to confirm the clinical implications of our pilot study.

We did not measure treatment exposure before study entry (except for recent antipsychotic drugs and cognitive therapy), so could not include this in our analyses. We did not correct for multiple comparisons (for example, using Bonferroni's correction); however, we had only one primary outcome, and because this is a pilot study, application of a more stringent alpha level for secondary outcomes would have been overly conservative. The use of acceptance into an early intervention service as an alternative to diagnosis as inclusion criteria might limit the generalisability of our findings to settings that do not have such specialist teams. Similarly, our exclusion of people who were in inpatient settings also limits generalisability to those with acute episodes needing hospital admission, and those who are referred to a clinical trial might not be representative of all participants who refuse drugs (although very few referred refused to participate). Our trial is also not likely to be generalisable to service users who are a great risk to themselves or the community, because they are likely to be managed with community treatment orders that require drug compliance. The absence of a control group that included non-specific factors such as contact time, warmth, and empathy, means that we cannot exclude the possibility that the recorded effects are due to such non-specific factors. Perhaps most importantly, our trial had low statistical power with a small sample size and a fairly high attrition rate. In view of the trend reported in trials of specific psychological therapies such as cognitive therapy for psychosis, which have shown that effect sizes are reduced when indices of study quality (such as adequate statistical power and active comparators) are controlled

for;<sup>16</sup> our effect sizes are probably inflated. Therefore, an adequately powered definitive randomised controlled trial is needed. A larger definitive trial would allow for analysis of factors such as therapist effects and subgroups (eg, participants not taking any drugs).

Our study has several clinical implications, although they should be considered cautiously in view of the limitations of a pilot study. Because the largest factor in our participants' choices not to take antipsychotics was side-effects,<sup>18</sup> alternative, evidence-based treatments should be available to people who choose not to take antipsychotics (panel). The offer of informed choices to service users who retain decision-making capacity might be possible if there is no risk to self or others, as judged on the basis of a comprehensive risk assessment. Such informed choices would benefit from a definitive trial that would increase confidence in the validity of our findings. We are not advocating that people who derive benefit from antipsychotic drugs should consider discontinuation; rather, we are advocating for evidence-based alternatives for those who choose not to on the basis of reasons that might include side-effects or perceived inefficacy (as many as half of all service users with schizophrenia spectrum disorders might choose not to take drugs<sup>5</sup>). A collaborative approach to decision making might improve the response for patients who choose to take antipsychotics, because the quality of relationship with the prescribing clinician is associated with attitudes to and adherence with drugs.<sup>38</sup> In this context, it is also worth noting that a fifth of our participants started antipsychotic drugs some point after having originally chosen not to. Consistent with this approach, the recently published NICE guidelines for psychosis and schizophrenia in children and young people recommend that service users and carers should be entitled to choose psychosocial interventions, such as cognitive therapy, in the absence of antipsychotics.<sup>36</sup>

**Contributors**

All authors were involved in the design of the study and the ongoing management and delivery of the trial, and all contributed to drafts of this manuscript. APM, the chief investigator, conceived the study, prepared the protocol, contributed to the training and supervision of the therapists and supervision of the researchers, had overall responsibility for the day-to-day running of the study, interpreted the data, took the lead on writing of the report, and is the guarantor for the study. APM, DT, PH, AB, RD, NC, TC, PC, TG, and VL participated in preparation of the treatment protocol and the training and supervision of the therapists. DT and AB managed the additional site. APM, MP, HS, and DT trained the researchers in the psychiatric interviews, and supervised and monitored standards of psychiatric interviewing and assessment throughout the trial. DT advised on diagnostic ratings and exclusions. MP was the trial manager and supervised and coordinated recruitment, contributed to training of research staff, and was responsible for staff management and overall coordination of the study. HS, LMD, AC, KI, and ST were responsible for maintaining reliability of assessment procedures and data collection. GD was the trial statistician and advised on randomisation and all statistical aspects of the trial, developed the analysis plan, and did the statistical analyses and is guarantor in this respect. LMD was the trial health economist. RB was a service-user consultant who took part in all aspects of the study. GD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Conflicts of interest**

APM, NC, PH, DT, TC, RD, PC, AB, TG, and VL are practitioners of cognitive therapy and deliver this intervention within the UK National Health Service. APM, DT, RD, and AB receive royalties from texts or books they have published on cognitive therapy. APM, DT, RD, PC, and AB have received fees for delivering workshops on cognitive therapy. DT has received lecture fees from pharmaceutical companies. All other authors declare that they have no conflicts of interest.

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**References**

- National Institute for Clinical Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. UK: NICE, 2009.
- Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; **374**: 620–27.
- Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; **379**: 2063–71.
- Lieberman JA, Stroup TS, McEvoy JP, et al, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353**: 1209–23.
- Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002; **63**: 892–909.
- Moncrieff J, Cohen D, Mason JP. The subjective experience of taking antipsychotic medication: a content analysis of Internet data. *Acta Psychiatr Scand* 2009; **120**: 102–11.
- Morrison AP, Hutton P, Shiers D, Turkington D. Antipsychotics: is it time to introduce patient choice? *Br J Psychiatry* 2012; **201**: 83–84.
- Lepping P, Sambhi RS, Whittington R, Lane S, Poole R. Clinical relevance of findings in trials of antipsychotics: systematic review. *Br J Psychiatry* 2011; **198**: 341–45.
- Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; **382**: 951–62.
- Correll CU, De Hert M. Antipsychotics for acute schizophrenia: making choices. *Lancet* 2013; **382**: 919–20.
- Ho B-C, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry* 2011; **68**: 128–37.
- Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; **360**: 225–35.
- Alvarez-Jiménez M, Hetrick SE, González-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry* 2008; **193**: 101–07.
- Owens GS, Richardson G, David AS, Szmukler G, Hayward P, Hotopf M. Mental capacity to make decisions on treatment in people admitted to psychiatric hospitals: cross sectional study. *BMJ* 2008; **337**: a448.
- Warner L, Mariathasan J, Lawton-Smith S, Samele C. A Review of the literature and consultation on choice and decision-making for users and carers of mental health and social care services. London: King's Fund/Sainsbury Centre for Mental Health, 2006.
- Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull* 2008; **34**: 523–37.
- Morrison AP, Hutton P, Wardle M, et al. Cognitive therapy for people with a schizophrenia spectrum diagnosis not taking antipsychotic medication: an exploratory trial. *Psychol Med* 2012; **42**: 1049–56.
- Morrison AP, Wardle M, Hutton P, et al. Assessing cognitive therapy instead of neuroleptics: rationale, study design and sample characteristics of the ACTION trial. *Psychosis* 2013; **5**: 82–92.
- Ainsworth JD, Harper RS. The PsyGrid experience: using web services in the study of schizophrenia. *Int J Healthc Inf Syst Inform* 2007; **2**: 1–20.
- Morrison AP. The interpretation of intrusions in psychosis: An integrative cognitive approach to hallucinations and delusions. *Behav Cogn Psychother* 2001; **29**: 257–76.
- Morrison AP, Renton JC, Dunn H, Williams S, Bentall RP. Cognitive therapy for psychosis: a formulation-based approach. London: Brunner-Routledge, 2004.
- Kingdon D, Turkington D. Cognitive therapy for schizophrenia. New York: Guilford Press, 2005.
- Blackburn IM, James I, Milne D, et al. The revised cognitive therapy scale (CTS-R): psychometric properties. *Behav Cogn Psychother* 2001; **29**: 431–46.
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261–76.
- Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1988; **23**: 99–110.
- Haddock G, McCarron J, Tarrrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* 1999; **29**: 879–89.
- Neil ST, Kilbride M, Pitt L, et al. The Questionnaire about the Process of Recovery (QPR): a research instrument developed in collaboration with service users. *Psychosis* 2009; **1**: 145–55.
- Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000; **101**: 323–29.
- Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behav Res Ther* 1997; **35**: 785–91.
- Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther* 1998; **36**: 455–70.
- Little RJA, Rubin DB. Statistical Analysis with Missing Data. London: John Wiley and Sons, 2002.
- Leucht S, Kissling W, Davis JM. The PANSS should be rescaled. *Schizophr Bull* 2010; **36**: 461–62.
- Leucht S, Davis JM, Engel RR, Kane JM, Wagenpfeil S. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology* 2007; **32**: 1903–10.
- Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry* 2011; **168**: 286–92.
- Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res* 2005; **79**: 231–38.
- National Institute for Clinical Excellence. Psychosis and schizophrenia in children and young people: Recognition and management. UK: NICE, 2013.
- Jones C, Hacker D, Cormac I, Meaden A, Irving CB. Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. *Cochrane Database Syst Rev* 2012; **4**: CD008712.
- Day JC, Bentall RP, Roberts C, et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. *Arch Gen Psychiatry* 2005; **62**: 717–24.