

# Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis (WIT): a parallel, single-blind, randomised controlled trial with a mediation analysis

Daniel Freeman, Graham Dunn, Helen Startup, Katherine Pugh, Jacinta Cordwell, Helen Mander, Emma Černis, Gail Wingham, Katherine Shirvell, David Kingdon



## Summary

**Background** Worry might be a contributory causal factor in the occurrence of persecutory delusions in patients with psychotic disorders. Therefore we postulated that reducing worry with cognitive behaviour therapy (CBT) would reduce persecutory delusions.

**Methods** For our two-arm, assessor-blinded, randomised controlled trial (Worry Intervention Trial [WIT]), we recruited patients aged 18–65 years with persistent persecutory delusions but non-affective psychosis from two centres: the Oxford Health National Health Service (NHS) Foundation Trust (Oxford, UK) and the Southern Health NHS Foundation Trust (Southampton, UK). The key inclusion criteria for participants were a score of at least 3 on the Psychotic Symptoms Rating Scale (PSYRATS) denoting a current persecutory delusion; that the delusion had persisted for at least 3 months; a clinical diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder; and a clinically significant level of worry. We randomly assigned (1:1) eligible patients, using a randomly permuted block procedure with variable block sizes and division by four strata, to either six sessions of worry-reduction CBT intervention done over 8 weeks added to standard care (the CBT-intervention group), or to standard care alone (the control group). The assessors were masked to patient allocations and did their assessments at week 0 (baseline), 8 weeks (end of treatment), and 24 weeks, follow-up. The primary outcomes were worry measured by the Penn State Worry Questionnaire (PSWQ) and delusions measured by the PSYRATS-delusion scale; we did the analyses in the intention-to-treat population, and also did a planned mediation analysis. This trial is registered with the ISRCTN Registry (number ISRCTN23197625) and is closed to new participants.

**Findings** From Nov 1, 2011, to Sept 9, 2013, we recruited 150 eligible participants and randomly assigned 73 to the CBT intervention group, and 77 to the control group. 143 patients (95%) provided primary outcome follow-up data. Compared with standard care alone, at 8 weeks the CBT intervention significantly reduced worry (mean difference 6.35 [SE 1.56] PSWQ units, 95% CI 3.30–9.40;  $p < 0.001$ ) and persecutory delusions (2.08 [SE 0.73] PSYRATS units, 95% CI 0.64–3.51;  $p = 0.005$ ). The reductions were maintained to 24 weeks follow-up. The mediation analysis suggested that the change in worry accounted for 66% of the change in delusion. No patients died or were admitted to secure units during our study. Six suicide attempts (two in the CBT intervention group, and four in the control group) and two serious violent incidents (one in each group) were noted, but no adverse events were deemed related to the treatments or the assessments.

**Interpretation** To our knowledge, this is the first large trial focused on persecutory delusions. We have shown that long-standing delusions were significantly reduced by a brief intervention targeted on worry, although the limitations for our study include no determination of the key elements within the intervention. Our results suggest that worry might cause paranoia, and that worry intervention techniques might be a beneficial addition to the standard treatment of psychosis.

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## Introduction

Treatments for psychotic disorders such as schizophrenia need substantial improvement. Our approach is to study single psychotic experiences such as persecutory delusions, establish a theoretical model, and translate the knowledge gained into treatment. To build the

treatment, one putative causal factor is taken at a time, changed, and the effect on the psychotic occurrence examined.<sup>1</sup> This approach is called an interventionist-causal model approach.<sup>2</sup> In this Article, we report the effects of targeting one causal factor—worry—in patients with persecutory delusions.

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Department of Psychiatry, University of Oxford, Oxford, UK (Prof D Freeman PhD, H Startup DPhil, K Pugh DCLinPsy, E Černis MSc); Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK and Medical Research Council NorthWest Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool, Liverpool, UK (Prof G Dunn PhD); Sussex Partnership NHS Foundation Trust, Research and Development Department, Mill View Hospital, Hove, UK (H Startup, K Pugh); and Academic Department of Psychiatry, Faculty of Medicine, University of Southampton, Southampton, UK (J Cordwell DCLinPsy, H Mander DCLinPsy, G Wingham BSc, K Shirvell MSc, Prof D Kingdon MD)

Correspondence to: Prof Daniel Freeman, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK  
[daniel.freeman@psych.ox.ac.uk](mailto:daniel.freeman@psych.ox.ac.uk)

Worry is an expectation of the worst happening. It consists of repeated negative thoughts about potential adverse outcomes, and is a psychological component of anxiety. Worry brings implausible ideas to mind, keeps them there, and increases the level of distress. Therefore we have postulated that worry is a causal factor in the development and maintenance of persecutory delusions, and have tested this theory in several studies.<sup>3-9</sup> We showed that levels of worry in patients with persecutory delusions are similar to those noted in generalised anxiety disorder;<sup>3</sup> a dose-response association exists between levels of worry and paranoia;<sup>4</sup> worry is a predictor of the occurrence and persistence of non-clinical paranoia in the general population<sup>5,6</sup> and in experimental settings;<sup>7</sup> and levels of worry predict the persistence of persecutory delusions.<sup>8,9</sup> Other study groups are also replicating and extending these findings.<sup>10,11</sup> We have translated this knowledge into treatment and shown in a pilot trial<sup>12</sup> that a brief intervention of worry-reduction added to standard care might lead to reductions in both worry and persecutory delusions. In the terminology of the scientific literature, worry in delusions is a so-called inus condition—“an insufficient but non-redundant part of an unnecessary but sufficient disorder.”<sup>13</sup> Persecutory delusions arise from a combination of causes, with each causal factor increasing the probability of such fears occurring.

We planned our trial as a rigorous test of these mechanistic links to inform both theory and treatment. A key mechanism (worry) was targeted. The appropriate control condition was a standard care group to establish that the mechanism had been successfully targeted, which would then allow examination of the effects of the mechanism change on the central clinical occurrence (persecutory delusions). We planned an elaborate mediation analysis to substantiate the postulated mechanism of delusion change. The aim of our study was to investigate whether the intervention with cognitive behaviour therapy (CBT) would reduce levels of worry in patients with persecutory delusions and reduce the delusions themselves; the improvements would be maintained at follow-up; and the reduction in worry would mediate changes in persecutory delusions.

## Methods

### Study design and participants

We did a randomised, controlled, single-blind trial in two UK centres: the Oxford Health National Health Service (NHS) Foundation Trust, Oxford, and the Southern Health NHS Foundation Trust, Southampton. These large mental health services cover populations of about 1.2 million people each. The trial received a favourable opinion from an NHS Research Ethics Service Committee, and the trial protocol has been published.<sup>14</sup> We sought referrals of patients aged 18–65 years with persecutory delusions from both centres. The inclusion criteria were: a current persecutory delusion as defined by Freeman and

Garety,<sup>15</sup> scoring at least 3 on the conviction scale of the Psychotic Symptoms Rating Scale (PSYRATS);<sup>16</sup> that the delusion had persisted for at least 3 months; a clinical diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder (ie, a diagnosis of non-affective psychosis); and a clinically significant level of worry, as shown by a score of more than 44 on the Penn State Worry Questionnaire (PSWQ).<sup>17</sup> Where major changes in drugs were going to be made, entry to the investigation would not occur until at least 1 month after stabilisation of dosage. Criteria for exclusion were: a primary diagnosis of alcohol or substance dependency or personality disorder; an organic syndrome or learning disability; a command of spoken English that was inadequate for engaging in therapy; and currently having individual CBT. All patients provided written informed consent.

### Randomisation and masking

We randomly assigned (1:1) eligible patients, after a baseline assessment, to either six sessions of CBT worry-reduction intervention done over 8 weeks added to standard care (the CBT intervention group), or to standard care alone (the control group). We used a web-based randomisation system, written by the Oxford Clinical Trials Unit for Mental Illness with a stratified randomisation procedure including four strata and a randomly permuted block procedure with variable block sizes. We did the stratification on the basis of centre and level of worry (defined as moderate when the PSWQ worry score was 44–62, and high when the score was  $\geq 63$ ).

The assessors were masked to patients' treatment allocations, but all patients were informed of their allocation by a trial therapist. Precautionary strategies included thinking about the best room to use and diary arrangements; patients being reminded by the assessors not to talk about allocation; and, after the initial assessment, the assessors did not look at clinical notes. If an allocation was revealed to the assessor, then remasking occurred, by use of another rater, which happened 11 times. However, if an allocation was revealed during an assessment session then these ratings were used: two 8-week assessments (both with the intervention) and four 24-week assessments (three with the intervention) were done unmasked.

### Procedures

We aimed to provide the CBT worry-reduction intervention in six sessions over 8 weeks. Each session lasted roughly an hour and took place in NHS clinics or at patients' homes. Therapy was delivered individually. Before therapy began the clinician met the patient for an initial introduction and assessment. The assessments of outcome measures were completed at 0 weeks (baseline), 8 weeks (end of therapy), and at 24 weeks (follow-up). Three graduate psychologists (EĈ, GW, and KS) did the enrolment and assessments.

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