Pilot of a randomised controlled trial of the selective serotonin reuptake inhibitor sertraline versus cognitive behavioural therapy for anxiety symptoms in people with generalised anxiety disorder who have failed to respond to low-intensity psychological treatments as defined by the National Institute for Health and Care Excellence guidelines

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Scientific summary

Sertraline vs. CBT for anxiety after no response to low-intensity treatments

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Scientific summary

Background

Generalised anxiety disorder (GAD) is characterised by excessive, uncontrollable and often irrational worry that interferes with daily functioning and can cause physical symptoms. It is common, but, as symptoms have to be present for at least 6 months for the diagnosis, it is often a chronic disorder when identified. It is often comorbid with depression or other anxiety or physical health disorders, worsening the prognosis. Rates of unemployment and social isolation are high, as GAD is associated with alcohol and substance misuse in an attempt by patients to relieve symptoms. People with GAD have a high number of general practitioner (GP) visits and secondary care contacts.

The most recent National Institute for Health and Care Excellence (NICE) guidelines established good evidence for the effectiveness of low-intensity psychological interventions in GAD. Step 1 interventions are usually delivered within primary care. If symptoms persist, referral to a step 2 low-intensity psychological intervention is recommended, usually facilitated by a low-intensity Improving Access to Psychological Therapies (IAPT) worker. However, a significant number of patients will not respond to these interventions and require 'stepping up' to more intensive step 3 interventions. According to NICE guidelines, the choice at step 3 is between a high-intensity psychological intervention [cognitive behavioural therapy (CBT)/applied relaxation] and a drug treatment.

The NICE Guidelines Advisory Group proposed sertraline as a first-choice pharmacological treatment, although it does not have a marketing authorisation for GAD and there are relatively few randomised trials. Nevertheless, in terms of risk of discontinuation as a result of adverse effects, sertraline was the best-tolerated antidepressant and its availability as a generic made it the most cost-effective choice.

There are a number of cognitive behavioural models of GAD. Dugas *et al.* (Dugas MJ, Gagnon F, Ladouceur R, Freeston MH. Generalized anxiety disorder: a preliminary test of a conceptual model. *Behav Res Ther* 1998;**36**:215–26) have developed a model known as the intolerance of uncertainty. This aims to help affected individuals develop beliefs about uncertainty that are less negative, rigid and pervasive. It has been tested in four published randomised clinical trials, with results indicating that it is more efficacious than waiting list control, supportive therapy and applied relaxation. This CBT model was therefore selected for this trial.

Although there is evidence of clinical effectiveness and cost-effectiveness of sertraline for GAD compared with placebo, and also of CBT compared with waiting list controls, there have been no head-to-head comparisons of sertraline [or any selective serotonin reuptake inhibitor (SSRI)] versus CBT to evaluate which treatment is more clinically effective and cost-effective. Current NICE guidelines suggest that the choice of treatment at step 3 between a pharmacological or psychological treatment should be based mainly on patient preference.

Aims and objectives

When assessing effectiveness of CBT or SSRIs for GAD, assessment of both clinical symptoms and functional impairment is important, as is assessment of outcomes for more than a few months, given that most pharmacological studies have follow-up periods of $\leq$ 12 weeks, and there is some evidence that CBT may have a protective effect against future episodes. Longer follow-up is crucial in making future recommendations, as longer-term costs of prescriptions and of the use of health-care resources are required to evaluate relative cost-effectiveness of the treatments. Our aim was to conduct a randomised controlled trial to compare the

clinical effectiveness and cost-effectiveness of a pharmacological treatment (the SSRI sertraline) prescribed at therapeutic doses, and a manualised psychological intervention (CBT) delivered by trained psychological therapists to patients with persistent GAD that had not improved with low-intensity psychological interventions as defined by NICE.

Hypothesis

We hypothesised that, in this population, CBT would lead to a greater improvement in GAD symptoms as measured by the primary outcome the Hospital Anxiety and Depression Scale – Anxiety component (HADS-A) at the 12-month follow-up than the prescription of sertraline in primary care in accordance with recommended clinical guidelines.

Primary aim

To assess clinical effectiveness at 12 months of treatment with the SSRI sertraline compared with CBT for patients with persistent GAD that had not improved with low-intensity psychological interventions.

Secondary aim

To calculate the cost-effectiveness at 12 months of treatment with sertraline compared with CBT for patients with persistent GAD that had not improved with low-intensity psychological interventions.

Objectives of internal pilot

At the recommendation of the Health Technology Assessment (HTA) programme commissioning board, we included a 12-month internal pilot with the following objectives:

1. to test and refine recruitment methods
2. to ascertain recruitment rates across pilot sites
3. to examine comorbidity between GAD, depression and other anxiety disorders
4. to ensure that the intervention could be delivered in accordance with the protocol in both arms
5. to monitor and assess follow-up rates of the completed primary outcome measure.

Methods

Recruitment was community based and linked with local IAPT services. We had four pilot sites, based in London (Camden and Islington, with Kingston) and Greenwich, Bristol, and Coventry and Warwickshire. If the internal pilot had been successful, we aimed to work with 15 sites across England in the full trial.

People not responding to step 2 low-intensity psychological interventions for their anxiety were reviewed by their low-intensity IAPT workers [psychological well-being practitioners (PWPs)]. Those scoring ≥ 10 on the Generalised Anxiety Disorder-7 (GAD-7) anxiety measure were given brief details about the trial and, if interested in possibly taking part, their permission sought for contact by the research team. The team offered them an assessment appointment and sent a full patient information sheet. With the patient's permission, their GP was contacted and asked to complete a Medical Suitability Review form to check that the patient had no known medical contraindications to sertraline if randomised to that intervention.

At baseline assessment it was checked that participants had received and understood the information sheet, and any queries had been answered. Informed consent was obtained before any trial procedures were performed. If they were happy to proceed, inclusion and exclusion criteria were checked. The Mini International Neuropsychiatric Interview (MINI) questionnaire was administered to check if participants fulfilled *Diagnostic and Statistical Manual of Mental Disorders 4th Edition* (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 4th Edition*. Washington, DC: American Psychiatric Association; 2000) criteria for GAD. Other significant comorbid anxiety disorders were noted, providing that the participant considered GAD their most important problem needing treatment, but comorbid major depression was an exclusion factor.

Inclusion criteria

- Age ≥ 18 years.
- Score of ≥ 10 on the GAD-7.
- Primary diagnosis of GAD diagnosed on the MINI questionnaire.
- Failure to respond to NICE-defined low-intensity interventions.

Exclusion criteria

- Inability to participate because of insufficient English or cognitive impairment.
- Current major depression.
- Comorbid anxiety disorder(s) causing greater distress.
- Significant dependence on alcohol or illicit drugs.
- Comorbid psychotic disorder.
- Receipt of antidepressants in the past 8 weeks or high-intensity psychological therapy within the past 6 months.
- Any contraindications to treatment with sertraline (including females of child-bearing potential agreeing to a pregnancy test at the assessment).

If all eligibility criteria were fulfilled, the researcher administered the Hamilton Anxiety Rating Scale (HAM-A) and asked the participant to complete baseline primary and secondary outcome measures. A copy of the completed baseline assessment form was forwarded to the chief investigator to confirm eligibility and, if confirmed, the participant was then randomised via an independent computerised service. The randomisation outcome was transmitted electronically to the trial manager, who contacted participants to inform them which treatment group they were in.

The research team also notified the patient's GP to inform them of the treatment allocation. If randomised to the medication arm, the patient was asked to make an appointment within the next 2 weeks to see their GP to discuss starting treatment with sertraline. The research team gave the relevant local IAPT services details of participants randomised to the CBT arm – the IAPT team then contacted the patient to arrange a course of treatment.

Interventions

1. Pharmacological (SSRI sertraline): potential participants were informed that sertraline, although not having current marketing authorisation for GAD, was recommended by NICE on the basis of its effectiveness in GAD clinical trials and had agreed to be prescribed this if so randomised. Sertraline was prescribed by the patient's GP in accordance with recognised clinical guidelines. GPs were asked to review these patients regularly (at least six times in 12 months) and patients were to take the medication for 1 year unless they had significant adverse effects. The GPs were given details of the suggested timing and content of these appointments with trial participants. The GP was asked to record any adverse events and both participants and GPs were asked to report any serious adverse events or suspected unexpected serious adverse reactions to the trial team.
2. Psychological (CBT): this was delivered by high-intensity therapists from local IAPT services trained to deliver 14 (± 2) 50-minute sessions of a manualised treatment developed for use in GAD, covering six treatment modules. A 2-day training course was provided for CBT therapists and their supervisors, and the supervisors had monthly expert supervision from two of the trial co-applicants in addition to the usual monthly clinical supervision given to the therapists. Procedures were agreed for a random 10% of sessions to be independently rated and reviewed for competence and adherence by an external expert.

Outcome measures

Primary outcome

The primary outcome was the HADS-A score at 12 months (this was a change from the original protocol stipulating the GAD-7, as we were unable to ask for the GAD-7 not to be routinely collected at each session in the CBT arm, which we had originally thought possible, and considered that this might be a source of potential bias).

Secondary outcomes

Secondary outcomes included HADS-A score at 3, 6 and 9 months; HAM-A score at 12 months; GAD-7 score at 6 and 12 months (all anxiety measures); Patient Health Questionnaire-9 (depression) and EuroQol-5 Dimensions, three-level version (used in health economic analysis) scores at 3, 6, 9 and 12 months; Work and Social Adjustment Scale score at 12 months (social functioning); Employment and Social Care questionnaire score (health economics) at 6 and 12 months; Client Satisfaction Questionnaire score at 3 and 12 months; and a patient preference scale score at 12 months. We planned to collect health service use data at baseline, for the preceding 6 months and at 12-month follow-up, recording GP consultations and psychotropic drug prescriptions, secondary care attendances and IAPT CBT session attendances.

Sample size calculation

Following estimates indicating standard deviations (SDs) of between 4 and 5 for the change in HADS-A scores between baseline and 12 months for both randomised conditions, we used an estimate of 5 for the SD of our outcome measure, with an additional component of variance to give an intracluster correlation coefficient of 0.02. With the conservative assumption of a cluster size of 7 and 20% for dropouts, we needed a sample size of 360 patients to detect a ('true') average difference of 2 between treatments with 90% power at $p < 0.05$ (two-sided).

Analysis

Principal analyses would have been conducted in accordance with a prespecified statistical analysis plan, finalised before database lock and conducted in accordance with the intention-to-treat principle using generalised mixed models. In the economic analysis we planned to calculate the net monetary benefit of CBT compared with sertraline for patients with persistent GAD who had not improved with step 2, low-intensity psychological interventions.

Results

Actual versus anticipated recruitment

We anticipated slow recruitment in the first 3 months of the internal pilot, but expected that this would improve as pilot sites became familiar with participant identification and recruitment processes. We had a projected total recruitment of 90 participants over the 12-month internal pilot, based on previous local IAPT data, with a target to achieve at least 70% (i.e. 63 participants at 1 year). Unfortunately, a very slow rate of recruitment meant that 7 months into the internal pilot in January 2016 we had recruited only seven participants as opposed to the projected 40, despite trying various strategies to improve recruitment rates.

Reasons for difficulties with recruitment

Fewer potential participants were identified by the PWPs than anticipated from our earlier IAPT data, and of 60 potential participants identified at screening 45 declined to participate – the majority ($n = 30$) because of reluctance to be randomised to receive medication. A further two were ineligible, two had GPs who declined to participate and four were identified after the decision had been made to close the trial.

Many PWPs described their clients being very anxious about the uncertainty of being referred and allocated to a random treatment. As a key component of GAD is worry about uncertainty, this is something we probably underestimated and illustrates the potential difficulty of recruiting participants to a randomised

controlled trial in GAD. Most potential participants identified were reluctant to consider randomisation to medication, and recruitment via a psychological therapy service was almost certainly biased towards people expecting to receive psychological therapy and therapists expecting to deliver this.

Strategies employed to improve recruitment

A number of methods were employed to attempt to improve identification of participants by PWPs. These included circulating materials to help them keep study recruitment in mind, funding lead PWPs to facilitate recruitment, meetings to discuss possible approaches to patients' queries or concerns, and database searches to identify possible cases both retrospectively and prospectively. Unfortunately, none of these resulted in improved recruitment.

Health Technology Assessment monitoring meeting

Because of poor recruitment, the funders organised a monitoring meeting in January 2016 at which the likely reasons were discussed and two possible further recruitment strategies presented: (1) a retrospective search of GP databases to identify people with anxiety/depression in primary care who might have GAD and could be approached about the trial; and (2) also identifying potential participants through a GP database search, but then assessing suitable patients for eligibility to take part in the trial and randomisation to either sertraline or high-intensity CBT within general practice without having to engage with a step 2 treatment delivered by PWPs.

The HTA programme committee was unsure about option (1) as it was seen to be an approach that would be unlikely to be generalisable within the NHS. Option (2), conducting the trial in primary care, was considered viable but a significant deviation from the original commissioning brief, and it was thought inequitable to proceed with this without reopening the application process. The decision was therefore made to close the trial prematurely.

Conclusions and recommendations

Recruiting to a head-to-head trial of medication versus high-intensity psychological therapy does not appear feasible in a psychological therapy service in which both patients and therapists are likely to be biased towards psychological therapies. An alternative strategy would be to conduct the trial within primary care, which is where initial choices are made between drug and psychological treatments. We would suggest that the HTA programme consider this option that, although not fitting directly with the NICE stepped-care model, fits more clearly with what generally happens in clinical practice.

Given the reluctance of patients to be randomised in this trial (both a reluctance to consider randomisation to the medication arm, but also because of uncertainty associated with randomisation, which people with GAD are likely to find particularly difficult) we would suggest that a naturalistic cohort patient-preference design should be considered if randomisation is not possible within primary care.

Trial registration

This trial is registered as ISCRTN14845583.

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The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

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