Antidepressant treatment with sertraline for adults with depressive symptoms in primary care: the PANDA research programme including RCT

Larisa Duffy,[1]* Gemma Lewis,[1] Anthony Ades,[2] Ricardo Araya,[3] Jessica Bone,[1] Sally Brabyn,[4] Katherine Button,[5] Rachel Churchill,[6] Tim Croudace,[7] Catherine Derrick,[2] Padraig Dixon,[2] Christopher Dowrick,[8] Christopher Fawsitt,[2] Louise Fusco,[8] Simon Gilbody,[4] Catherine Harmer,[9] Catherine Hobbs,[5] William Hollingworth,[2] Vivien Jones,[2] Tony Kendrick,[10] David Kessler,[2] Naila Khan,[8] Daphne Kounali,[2] Paul Lanham,[11] Alice Malpass,[2] Marcus Munafo,[12] Jodi Pervin,[4] Tim Peters,[2] Derek Riozzie,[11] Jude Robinson,[13] George Salaminios,[1] Debbie Sharp,[2] Howard Thom,[2] Laura Thomas,[2] Nicky Welton,[2] Nicola Wiles,[2] Rebecca Woodhouse[4] and Glyn Lewis[1]

[1]Division of Psychiatry, University College London, London, UK
[2]Bristol Medical School, University of Bristol, Bristol, UK
[3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[4]Department of Health Sciences, University of York, York, UK
[5]Department of Psychology, University of Bath, Bath, UK
[6]Centre for Reviews and Dissemination, University of York, York, UK
[7]School of Nursing and Health Studies, University of Dundee, Dundee, UK
[8]Institute of Psychology Health and Society, University of Liverpool, Liverpool, UK
[9]Department of Psychiatry, University of Oxford, Oxford, UK
[10]Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
[11]Patient and public involvement contributor, UK
[12]Department of Psychology and Integrated Epidemiology Unit, University of Bristol, Bristol, UK
[13]Department of Sociology, Social Policy and Criminology, University of Liverpool, Liverpool, UK

*Corresponding author larisa.duffy@ucl.ac.uk

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Scientific summary

The PANDA research programme including RCT

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Scientific summary

Background

There were over 70 million antidepressent prescriptions in England in 2018, with a substantial cost to the NHS. Selective serotonin reuptake inhibitors are the first-line antidepressant recommended by UK National Institute for Health and Care Excellence guidelines. However, there is little clinical guidance on when an antidepressant should be prescribed, uncertainty about when patients might benefit and concerns that antidepressants are prescribed unnecessarily.

Aims and objectives

The overall aim of the PANDA (What are the indications for Prescribing ANtiDepressAnts that will lead to a clinical benefit?) research programme was to provide general practitioners with improved guidance that would enable them to make recommendations about the probable response to antidepressants for patients with depressive symptoms. We wanted to estimate the minimal clinically important difference for depressive symptom questionnaires and understand more about how patients respond to such assessments. We carried out a randomised controlled trial (the PANDA randomised controlled trial) that examined the cost-effectiveness of sertraline compared with placebo. Our hypothesis was that the response to antidepressants compared with placebo would increase with both the severity and duration of depressive symptoms. We conducted our research in three phases.

Methods and results

Phase 1: using previously collected data

Aim 1a: using existing data to estimate the minimal clinically important difference for the Beck Depression Inventory, version 2

We examined data from three existing randomised controlled trials [GENetic and clinical Predictors Of treatment response in Depression (GenPod), TREAting Depression with physical activity (TREAD) and Clinical effectiveness and cost-effectiveness of cognitive Behavioural Therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care (CoBalT)], which used a Global Rating of Change question and the Beck Depression Inventory, version 2, to measure depressive symptoms. We estimated the minimal clinically important difference by calculating the reduction in Beck Depression Inventory, version 2, scores in those who reported they had improved. We found evidence that the minimal clinically important difference increased as the initial severity of depressive symptoms rose and the minimal clinically important difference was better described as a percentage reduction of the initial score rather than an absolute fixed value. Our estimates of minimal clinically important difference were a 17%, 18% and 32% reduction for people with depression for GenPod, TREAD and CoBalT, respectively.

Aim 1b: 'mapping' the relationship between different depression scales

We identified 31 RCTs that had included more than one depressive symptom, or health-related quality-of-life scales. We used a novel method to compare the relative responsiveness of the scales that allowed estimation of mapping coefficients that could translate treatment effects. We found evidence that, of the depression measures, the Patient Health Questionnaire-9 items was the most responsive to change. A 1.0 standard deviation treatment effect on the Beck Depression Inventory (the reference) was, on average, equivalent to 1.52 standard deviations on the Patient Health Questionnaire-9 items (95% credibility interval 1.17 to 2.05 standard deviations) and 1.31 standard deviations on the Hamilton Rating Scale for Depression (95% credibility interval 1.04 to 1.69 standard deviations).

Aim 1c: value-of-information study to estimate the probable benefit of carrying out the PANDA randomised controlled trial

We developed a novel economic model that incorporates the severity of depression as part of the decision-making process. The model determined that treating patients with a severity score of ≥ 2 on the Hamilton Rating Scale for Depression had the highest probability (> 65%) of being cost-effective at a £20,000 willingness-to-pay threshold. However, there was a lack of evidence at low levels of severity, and the results relied on a number of assumptions. We concluded that the PANDA randomised controlled trial was likely to be an efficient use of resources to reduce uncertainty in the most cost-effective treatment for such patients (expected value of partial perfect information = £67.7M over a 10-year time horizon).

Phase 2: cohort study: using both quantitative and qualitative methods

We conducted a cohort study of 558 people who had presented with symptoms of depression or low mood to their general practitioner in the previous 12 months. Practices were recruited in Bristol, Liverpool and York. Potential participants were identified by searching the general practitioner electronic records and were then invited to participate if they were aged 18–70 years and did not have comorbid psychosis, bipolar disorder, eating disorders or substance dependence. Participants were followed up at 2, 4 and 6 weeks after baseline, when they completed self-administered questionnaires assessing symptoms of depression and anxiety (i.e. Beck Depression Inventory, version 2, Patient Health Questionnaire-9 items and Generalised Anxiety Disorder-7) and were asked to rate their own improvement using a Global Rating of Change question. The Global Rating of Change was assessed by asking patients 'compared to when we last saw you 2 weeks ago, how have your moods and feelings changed?'. Response options were 'I feel a lot better' (1), 'I feel slightly better' (2), 'I feel about the same' (3), 'I feel slightly worse' (4), or 'I feel a lot worse' (5). The Clinical Interview Schedule – Revised was completed at baseline.

Aim 2a: estimates of the minimal clinically important difference in commonly used self-administered questionnaires for depressive symptoms

In the PANDA cohort, we estimated the optimal threshold score for the Patient Health Questionnaire-9 items, Beck Depression Inventory, version 2, and Generalised Anxiety Disorder-7 (a measure of anxiety symptoms), below which someone was more likely to report feeling better. This as the most robust estimate of minimal clinically important difference as it also takes account of the variability of scores. The PANDA cohort had a lower range of scores than those found in the previous analysis (see *Aim 1a: using existing data to estimate the minimal clinically important difference for the Beck Depression Inventory, version 2*) and we found that the size of the minimal clinically important difference, expressed as proportional reduction, was larger for when initial severity of depressive symptoms was low. For those with an initial score of 12 on the Patient Health Questionnaire-9 items, the minimal clinically important difference was 19.7%, but for those with an initial score of 4, the minimal clinically important difference was 48.2%.

Aim 2b: investigation of the changes reported by patients as they recover from depression

Study 1: usefulness of the Patient Health Questionnaire-9 items in primary care to determine meaningful symptoms of low mood – a qualitative study

We conducted a longitudinal qualitative study of 18 participants selected using the same criteria as the PANDA cohort but with a purposive sampling strategy. The participants completed the Global Rating of Change and the Patient Health Questionnaire-9 items using cognitive interviewing techniques at 2, 4 and 6 weeks after baseline. Participants reported that the Patient Health Questionnaire-9 items omits certain symptoms that are important to people with depression. Participants translated the options on frequency such that 'several days' was used to represent a higher intensity of symptom. Participants thought that the Global Rating of Change was a good way of taking account of all the symptoms and changes that were important to them.

Study 2: variation in recognition of happy and sad facial expressions and self-reported depressive symptom severity

Biases in the way that people process emotional information might be markers of recovery from depression and it has been suggested that antidepressants work via their action on emotion-processing. In the PANDA cohort, we administered a task concerned with identifying the emotional expression on morphed faces. We found that depressive symptoms were associated with an increase in reporting happy faces when ambiguous expressions were presented. There was no association between depressive symptoms and recognition of sad faces.

Study 3: variation in the recall of socially rewarding information and depressive symptom severity – a prospective cohort study

We investigated whether or not severity of depressive symptoms in the PANDA cohort was associated with recall of positive and negative words, as a measure of emotional processing. We found evidence that, for every increase in two positive words recalled, depressive symptoms were lower by –0.6 (95% confidence interval –1.0 to –0.2) Beck Depression Inventory points, but there was no evidence for an association with negative words. These findings suggest that people with more severe depressive symptoms recall less positive information but negative information is unaffected, which is similar to the face recognition findings above.

Aim 2c: to investigate disagreement between self-reported improvement and changes in the scores on depressive symptom questionnaires

Study 1: why are there discrepancies between depressed patients' Global Rating of Change and scores on the Patient Health Questionnaire-9 items depression module? A qualitative study of primary care in England

We identified participants from the PANDA cohort who reported a disagreement between the Global Rating of Change and the change in scores on the Patient Health Questionnaire-9 items. We defined disagreement as meaningful if scores changed by ≥ 15%, based on preliminary results. Of the first 86 participants from the Liverpool site, 29 participants (34%) with the most pronounced disagreement took part in this qualitative study. We identified four themes used by participants to explain the mismatch between the Global Rating of Change and the Patient Health Questionnaire-9 items: (1) problems with the Patient Health Questionnaire-9 items and perceptions that the Global Rating of Change provided a more accurate assessment of current mental state, (2) the impact of recent positive or negative life events, (3) personal understanding of depression and coping mechanisms and (4) an inability to recall how they felt in the past.

Study 2: changes in self-administered measures of depression severity and patients' own perceptions of changes in their mood – a cohort study in primary care

This quantitative study in the PANDA cohort investigated the disagreement between changes in Patient Health Questionnaire-9 items and Beck Depression Inventory, version 2, scores and responses to self-reported improvement (Global Rating of Change). We used a minimal clinically important difference estimate of 20%. We found that in a substantial proportion of patients (51% on the Patient Health Questionnaire-9 items scale and 55% on the Beck Depression Inventory, version 2, scale), there was a clinically important disagreement between their responses to the questionnaires and the Global Rating of Change. We found that participants who reported anxiety and poor quality of life were less likely to report feeling better on the Global Rating of Change after taking account of their change in depressive symptom score.

Phase 3: randomised controlled trial

Aim 3: severity and duration of depressive symptoms and response to antidepressants (the PANDA trial) – a pragmatic randomised controlled trial in primary care

We conducted a pragmatic randomised multicentre double-blind placebo-controlled trial of patients from 179 primary care surgeries in four UK sites. Patients aged 18 to 74 years with reported depressive symptoms were eligible if there was uncertainty about the benefit of an antidepressant. Patients were

individually randomised to 100 mg daily of sertraline or placebo. The primary outcome was the Patient Health Questionnaire-9 items score at 6 weeks. Secondary outcomes at 2, 6 and 12 weeks were depressive symptoms and remission assessed using the Patient Health Questionnaire-9 items and the Beck Depression Inventory, version 2, generalised anxiety disorder, mental and physical health-related quality of life, global ratings of change, health-care costs and quality-adjusted life-years.

Our primary outcome analyses were of 550 patients (sertraline, $n = 266$; placebo, $n = 284$). The mean Patient Health Questionnaire-9 items score at 6 weeks was 7.98 (standard deviation 5.63) in the sertraline group and 8.76 (standard deviation 5.86) in the placebo group. In the sertraline group, Patient Health Questionnaire-9 items scores were 5% (95% confidence interval –7% to 15%; $p = 0.41$) lower than in the placebo group. There was no evidence that the treatment effect on the primary outcome varied according to depression severity or duration. Of the secondary outcomes, there was strong evidence that sertraline reduced anxiety symptoms (Generalised Anxiety Disorder-7 score reduced by 17%, 95% confidence interval 9% to 25%; $p = 0.00005$), improved mental, but not physical, health-related quality of life and self-reported global improvement. There was weak evidence that depressive symptoms were reduced by sertraline at 12 weeks for both the Patient Health Questionnaire-9 items and the Beck Depression Inventory, version 2, scales. There was some evidence that sertraline was more cost-effective than the placebo at a threshold of £20,000 (incremental net monetary benefit £118, 95% confidence interval –£23 to £260) per quality-adjusted life-year. Sertraline had a high probability (> 90%) of being cost-effective if the health system was willing to pay > £20,000 per quality-adjusted life-year gained. We did not find evidence for any influence of severity of symptoms or duration on treatment response or cost-effectiveness, but our analysis had low statistical power.

Conclusions

Use of self-administered questionnaires in assessing depressive symptoms

There is a strong correlation between changes in Patient Health Questionnaire-9 items score and self-reported improvement using the Global Rating of Change, and the Patient Health Questionnaire-9 items appeared to be better at detecting average change than the Beck Depression Inventory, version 2, scale and the Hamilton Rating Scale for Depression. However, we identified substantial disagreement between the Global Rating of Change and changes in Patient Health Questionnaire-9 items score when considering individual responses. Up to half of the people in our sample reported a disagreement between the Global Rating of Change and changes on the Patient Health Questionnaire-9 items. Our qualitative research also pointed out the limitation of these scales and supported the validity of the Global Rating of Change in providing an overall measure of improvement. We conclude that the Patient Health Questionnaire-9 items should not be used on its own to assess individual change. It is important for clinicians to supplement results from the Patient Health Questionnaire-9 items with additional clinical assessment including open-ended questions about any improvements.

We have estimated the minimal clinically important difference for the Beck Depression Inventory, version 2, Patient Health Questionnaire-9 items and Generalised Anxiety Disorder-7 using a patient anchoring approach in which we use the Global Rating of Change to estimate the threshold below which someone is more likely to regard themselves as having improved. At higher initial severity, we found a minimal clinically important difference of about 20%. However, at lower severities, the minimal clinically important difference increased as a proportion; so for the lowest severity we examined, the minimal clinically important difference was as large as 50% for the Patient Health Questionnaire-9 items. Our estimates were also imprecise at the lower severities. This complex relationship between initial severity and minimal clinically important difference is an important finding.

Effectiveness and cost-effectiveness of sertraline

The PANDA randomised controlled trial did not find evidence that sertraline led to a clinically important reduction in depressive symptoms at 6 weeks. However, we found strong evidence at 6 and 12 weeks that sertraline reduced anxiety symptoms, that mental health-related quality of life improved and that participants reported feeling better. There was some weak evidence that sertraline reduced depressive symptoms at 12 weeks. Sertraline is an inexpensive intervention that had a high probability (> 90%) of being cost-effective compared with placebo at 12 weeks. Our results of an improvement in anxiety symptoms are to be expected given previous findings, but the lack of an early effect on depressive symptoms is unexpected. We think that the most likely explanation for this is that previous trials have mostly used the Hamilton Rating Scale for Depression or similar measures of depression. The Hamilton Rating Scale for Depression is a relatively unstandardised measure in which the observer can alter questions and it requires judgements; therefore, this might have led to a halo effect on the rating of depressive symptoms because participants reported feeling better as anxiety symptoms had reduced. We could not find evidence that the treatment response to sertraline or cost-effectiveness varied according to severity or duration, but these analyses had low power.

We can apply our minimal clinically important difference results to the PANDA randomised controlled trial. At 6 weeks' follow-up, our findings suggest that there was a 5% (95% confidence interval –7% to 15%) reduction in Patient Health Questionnaire-9 items scores and a 21% (95% confidence interval 11% to 30%) reduction in Generalised Anxiety Disorder-7 scores. The relevant minimal clinically important difference for Patient Health Questionnaire-9 items is 21% and for Generalised Anxiety Disorder-7 is 27%. We can therefore conclude that, on average, sertraline does not lead to a clinically important difference in depressive symptoms at 6 weeks, but the effect on anxiety symptoms is more consistent with such a clinically important effect. A further implication from our minimal clinically important difference results is that, for those who expect to have low scores at follow-up, the minimal clinically important difference is very large. About 30% of the PANDA randomised controlled trial placebo group had a Generalised Anxiety Disorder-7 score of ≤ 3 at follow-up, which suggests that they would not have benefited from sertraline if they had received that treatment.

An alternative approach would be to estimate the proportion who reported 'feeling better' using our self-reported improvement question. This allows estimation of the number needed to treat. The number needed to treat at 6 weeks was 8.5 (95% confidence interval 5.2 to 22.1) participants and at 12 weeks 6.4 (95% confidence interval 4.6 to 10.3) participants.

Trial registration

This trial is registered as ISRCTN84544741 and EudraCT number 2013-003440-22.

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Editorial contact: journals.library@nihr.ac.uk

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