Title: Cost Effectiveness of Pharmacological Treatments for Generalized Anxiety Disorder

Authors: Ifigeneia Mavranezouli,[1] Nick Meader,[1,2] John Cape,[3,4] and Tim Kendall[4,5,6]

1 National Collaborating Centre for Mental Health, Centre for Outcomes Research and Effectiveness, Research Department of Clinical, Educational & Health Psychology, University College London, London, UK

2 Current affiliation: Centre for Reviews and Dissemination, University of York, UK

3 Camden and Islington NHS Foundation Trust, London, UK

4 Research Department of Clinical, Educational and Health Psychology, University College London, London, UK

5 National Collaborating Centre for Mental Health, Royal College of Psychiatrists, London, UK

6 Sheffield Health and Social Care, NHS Foundations Trust, Sheffield, UK

Correspondence to: Dr Ifigeneia Mavranezouli, National Collaborating Centre for Mental Health, BPS-CORE, Research Department of Clinical, Educational & Health Psychology, UCL, Gower Street, London WC1E 6BT, UK; tel: +44(0)207 679 1964; fax: +44(0)207 91 68 511; e-mail: i.mavranezouli@ucl.ac.uk

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Abstract (wordcount 344)

Background: Generalized anxiety disorder is one of the most prevalent anxiety disorders with important implications for patients and healthcare resources. However, few economic evaluations of pharmacological treatments for generalized anxiety disorder have been published to date, and those available have assessed only a limited number of drugs.

Objective: To assess the cost effectiveness of pharmacological interventions for patients with generalized anxiety disorder in the UK.

Methods: A decision-analytic model in the form of a decision-tree was constructed to compare costs and QALYs of six drugs (duloxetine, escitalopram, paroxetine, pregabalin, sertraline and venlafaxine-XL) and 'no pharmacological treatment' used as first-line pharmacological treatments in people with generalized anxiety disorder. The analysis adopted the perspective of the National Health Service and Personal Social Services in the UK. Efficacy data were derived from a systematic literature review of double-blind, randomized controlled trials and were synthesised using network meta-analytic techniques. Two network meta-analyses were undertaken to assess the comparative efficacy (expressed by response rates) and tolerability (expressed by rates of discontinuation due to intolerable side effects) of the six drugs plus 'no treatment' in the study population. Cost data were derived from published literature and national sources, supplemented by expert opinion. The price year was 2011. Probabilistic sensitivity analysis was conducted to evaluate the underlying uncertainty of the model input parameters.

Results Sertraline was the best drug in limiting discontinuation due to side effects and the second best drug in achieving response in patients not discontinuing treatment due to side effects. It also resulted in lowest costs and highest number of QALYs among all treatment options assessed. Its probability of being the most cost-effective drug reached 75% at a willingness-to-pay of £20,000 per extra QALY gained.

Conclusion Sertraline appears to be the most cost-effective drug in the treatment of patients with generalized anxiety disorder. However, this finding is based on limited evidence for sertraline (two published trials). Sertraline is not licensed for the treatment of generalized anxiety disorder in the UK, but is commonly used by primary care practitioners for the treatment of depression and mixed depression and anxiety.

Key messages

- Our network meta-analysis indicates that, in the pharmacological treatment of generalised anxiety disorder, sertraline is the best drug in reducing discontinuation due to intolerable side effects and duloxetine is the best drug in achieving response in those patients who do not discontinue treatment due to intolerable side effects.

- The economic analysis suggests that sertraline is likely to be the most cost-effective pharmacological treatment option for generalized anxiety disorder

Generalized anxiety disorder (GAD) is one of the most common mental disorders in primary care[1] with a lifetime prevalence estimated to range between 0.8% and 12.7% worldwide.[1-3] Besides anxiety and worry about a range of everyday isssues, patients with GAD experience other psychological symptoms such as irritability, poor concentration and sleep disturbance. A number of somatic symptoms can also be present in patients with GAD, including sweating, dry mouth, palpitations, shortness of breath, dizziness, headaches and aching pains.[4] GAD is frequently comorbid with other mental health disorders, especially depressive disorders (major depression and dysthymia), other anxiety disorders (especially panic disorder, social phobia and specific phobias) and somatoform disorders, as well as with substance misuse.[1;3;5;6]

In addition to the psychological burden to patients, GAD imposes a significant economic burden to society, due to high utilisation of healthcare resources, particularly primary health services, and to significant productivity losses.[7;8] Using data from the National Comorbidity Study, the annual total cost associated with anxiety disorders in the US was estimated at $42.3 billion in 1990, or $1542 per patient.[9] Of the total cost, 54% was attributed to nonpsychiatric medical treatment, 31% was incurred by psychiatric treatment, 10% involved productivity losses primarily due to reduced productivity rather than absenteeism, 3% related to mortality costs, and 2% comprised prescription pharmaceutical costs.[9] In Europe, the average cost per case diagnosed with GAD was estimated at €1804 in 2004, with country-specific estimates ranging from €531 (Estonia) to €3238 (Switzerland).[10] GAD was associated with the highest cost per case in Europe among other anxiety disorders under study: obsessive compulsive disorder,

specific phobia, social phobia, agoraphobia, and panic disorder incurred a cost per case that ranged between €350 and €967.[10]

Management of patients with GAD includes provision of psychological therapies (such as supportive psychotherapy and cognitive behavioural therapy) and pharmacological interventions, mainly selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI).[11] Benzodiazepines and buspirone are also used in the treatment of GAD, but are recommended for short-term use only (up to 2 to 4 weeks).[12]

So far only few published economic evaluations of pharmacological treatments for GAD are available, assessing a very limited number of drugs.[13-17] Given the variety of drugs that are currently available for the treatment of GAD, the significant expenditure associated with provision of antidepressants (£220.3 million in England in 2010),[18] and the imperative need for efficient use of healthcare resources especially under conditions of restricted budgets, the objective of this study was to examine the cost-effectiveness of pharmacological interventions used in the long-term treatment (i.e. beyond 4 weeks) of patients with GAD from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) in the UK, using decision-analytic modelling. The economic analysis presented in this paper is an update of the analysis that was undertaken during the development of national guidance for people with GAD

in England and Wales, commissioned by the National Institute for Health and Clinical Excellence (NICE).[19] For the current analysis we updated the guideline systematic review on pharmacological treatments for patients with GAD; moreover, unit costs were updated to represent 2011 values.

The selection of drugs considered in the analysis was determined by the availability of relevant clinical data and further interpretation of the data by clinical experts in the field (that is, by the members of the Guideline Development Group -GDG-), who advised on the appropriateness of specific drugs for use as first-line pharmacological treatments in patients with GAD. Drugs that have been found to be effective in the treatment of GAD, either licensed or commonly used for this purpose, have an acceptable risk-to-benefit ratio and are appropriate for use beyond 4 weeks, were considered in the economic analysis. The following pharmacological treatment options were thus assessed: escitalopram, paroxetine and sertraline (SSRIs); duloxetine and venlafaxine XL (SNRIs.); pregabalin (antiepileptic); and 'no pharmacological treatment'; the latter represented the placebo arm of the trials used to populate the economic analysis and was included in the analysis in order to assess whether pharmacological treatments are cost-effective versus a baseline treatment without drug use in patients with GAD.

Clinical evidence considered in the economic analysis was synthesised using network meta-analytic techniques, which enable evidence synthesis from both direct and indirect

comparisons between drugs, and allow simultaneous inference on all drugs examined in trial pair-wise comparisons while preserving randomisation.[20;21] The measure of outcome for the economic analysis was the Quality Adjusted Life Year (QALY). Resource use estimates were based on data from a national survey on psychiatric morbidity[22] supplemented with expert (GDG) opinion, and were subsequently combined with national unit costs to produce total costs associated with each treatment option assessed.

Methods

Economic model structure

A decision-analytic model in the form of a decision-tree was constructed to estimate the costs and outcomes (in the form of QALYs) of seven hypothetical cohorts of patients with GAD initiated on each of the seven treatment options assessed. The structure of the model and the health states considered were dictated by the treatment patterns of GAD and the associated care pathways in the UK, the natural history of the disease, as well as the availability of relevant clinical data (for example, 'response to treatment' rather than 'remission' was considered in the model structure, as the former was more consistently reported across pharmacological trials in GAD; moreover, available utility data referred to the health state of response but not to that of remission, as described in the relevant section of methods). Patients in the cohorts receiving a drug either continued their first-line drug for 8 weeks, or discontinued due to intolerable side effects.

Patients who continued and responded to first-line drug treatment were then given maintenance treatment consisting of the same drug for a period of 6 months (26 weeks), during which they might experience a relapse. Patients discontinuing the first-line drug due to intolerable side effects or not responding to it were switched to a second-line drug, which was a mixture of all drugs assessed in the model (in terms of costs and clinical outcomes), excluding the first-line drug in that cohort. Patients receiving the second-line drug were assumed to continue treatment and to experience the same events as those associated with first-line pharmacological treatment (that is, no response or response and maintenance treatment, during which they might relapse). Patients in the 'no pharmacological treatment' cohort either discontinued treatment without clinically improving ('no response'), or continued their treatment and experienced the same events with people under pharmacological treatment. The time horizon of the analysis was 42 weeks, based on the optimal duration of initial pharmacological treatment (8 weeks) and maintenance treatment (26 weeks), and in order to allow for switching to second-line treatment in case patients were not responsive to their 8-week first-line treatment. The model was constructed using Microsoft Office Excel 2007. A schematic diagram of the decision-tree is presented in Figure 1.

Clinical data utilised in the model

A. Systematic literature review,

A systematic literature review was performed for the NICE guideline, which included double-blind RCTs that assessed the benefits and harms of pharmacological interventions for the treatment of people with GAD as defined in DSM-III-R or DSM-IV. The following electronic databases were searched from inception to 9 May 2010: MEDLINE, EMBASE, CINAHL, PsychINFO and the Cochrane Library. Details on the search strategy, the methods and the inclusion criteria for the review are provided in the full guideline.[19] For the current study, we updated the searches to include eligible studies published up to 21 March 2012.

B. Clinical outcomes considered

Two main clinical outcomes were utilised in the economic model: treatment discontinuation due to intolerable side effects (reflecting tolerability); and *conditional* response, defined as 50% or above reduction in the Hamilton rating scale for Anxiety (HAM-A) score in patients *not* discontinuing treatment due to side effects. It must be noted that the majority of studies in the systematic review of clinical literature defined response as a ≥ 50% reduction in HAM-A score. A limited number of RCTs that reported response data but used different clinical measures to determine response were not considered in the economic analysis for consistency purposes and in order to avoid bias.

C. Methods of evidence synthesis

Data on the two main outcomes considered in the economic model were synthesised using network meta-analytic techniques. Network meta-analyses were conducted within

a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.[23;24] Two separate network meta-analyses were conducted using a full random-effects model that was based on hazards rather than probabilities, to account for the different follow-up times of the studies included in the meta-analyses. The model is a simplification of a “competing risks” model developed for the meta-analysis of multiple mutually exclusive outcomes that assumes constant hazard for each outcome in each study over time.[25] The probability of the outcome in each meta-analysis was modelled using a binomial likelihood.[20] A further model was used in each analysis to predict the baseline placebo effect on discontinuation due to side effects and on conditional response, respectively, in a new trial, based on the respective evidence from placebo arms of the RCTs included in the systematic review. Treatment effects of all drugs versus placebo were then modelled on the log-hazard rate scale. The output of the two network meta-analyses that was used in the economic analysis comprised the probability of discontinuation due to intolerable side effects and the probability of conditional response for each drug (plus placebo, the data for which were used to populate the ‘no pharmacological treatment’ arm of the model) by the end of 8 weeks, i.e. the optimal period of initial pharmacological treatment and the average time horizon of the studies considered in the two network meta-analyses. The Winbugs code used to conduct the two network meta-analyses is provided in Supplemental Digital Content 1. In each meta-analysis, an initial burn-in period of 60,000 iterations was followed by 300,000 further iterations, of which every 30th was retained; consequently, 10,000 posterior simulations were recorded for each meta-analysis.

Uninformative prior parameters were chosen for both models. Two different sets of initial values were used in each model (i.e. two chains were specified), and convergence was tested by visual inspection of the Brooks Gelman-Rubin diagram. In addition, convergence of the models was assessed by checking the autocorrelation and the Kernel density plots within WinBUGS.

The two sets of network meta-analyses utilised in total data on 13,508 patients from 39 RCTs.[26-64] These 39 trials provided direct or indirect evidence on discontinuation due to intolerable side effects between the 7 treatment options assessed in the economic analysis; of these, 26 RCTs with 9,717 participants provided also direct or indirect evidence on conditional response between the 7 treatments. In every arm of each trial, the rate of conditional response was estimated as the number of patients responding to treatment, divided by the total number of patients after excluding those who discontinued due to intolerable side effects. A small number of RCTs included in the guideline systematic review reported response data but did not provide data on discontinuation due to intolerable side effects. Consequently, it was not possible to extract data on conditional response from these studies, which were therefore not considered in the respective network meta-analysis. The baseline (placebo) probabilities of discontinuation due to side effects and of conditional response were based on respective estimates made for a new (hypothetical) trial, that were predicted following meta-analysis of the placebo arms of the relevant RCTs utilised in the 2 network meta-analyses; the placebo arms of another 3 placebo-controlled trials that

were identified in the guideline systematic review were also added in this dataset.[65-67]

All data utilised in the two sets of meta-analyses are provided in Supplemental Digital Content 2. The respective evidence networks are shown in Figures 2 and 3.

D. Other clinical input parameters

The probability of response for the second line drug in each decision node of the model was calculated as the average probability of conditional response of all drugs considered in the analysis except the one that was used as first-line treatment in this particular node of the model; the probability of relapse following response to 'no pharmacological treatment' and the relative risk of the probability of relapse following response to drug treatment versus placebo (no treatment) were estimated based on the updated meta-analysis of relevant RCTs that was originally included in the guideline systematic review.[68-73]

Utility data considered in the model

A systematic search of the literature identified two studies that reported utility data for specific health states associated with GAD[74;75] Allgulander et al[74] generated utility scores using SF-36 data derived from 273 people with GAD participating in a double-blind, placebo-controlled, relapse prevention, multinational clinical trial of

escitalopram.[68] Participants (who were included in the trial if they had a HAM-A total score of 20 or more) first received 12 weeks of open-label treatment with escitalopram. Those responding to treatment were then randomised to double-blind treatment with escitalopram or placebo aiming at relapse prevention. Response to treatment was defined as a HAM-A score of 10 or less; relapse was defined as a HAM-A total score 15 or more or lack of efficacy, as judged by the investigator. SF-36 data were taken from participants at the end of the open-label period, and at the end of, or at last assessment during, the double-blind period. SF-36 scores were converted into utility scores using the SF-6D algorithm.[76] The utility data from this study were selected for use in the economic analysis because they corresponded to the health states described in the economic model (that is, response, non-response, relapse following response, and no relapse following response). In contrast, the utility data by Revicki et al.[75] corresponded to the states of asymptomatic, mild, moderate and severe anxiety and therefore could not be matched to the health states considered in the economic model. The economic analysis assumed linear changes in utility between the start of the model and the end of the 8-week period of initial treatment; and over the 26-week period of maintenance treatment.

Side effects from medication are expected to result in a reduction in utility scores of patients with GAD. Side effects consist mainly of nausea, insomnia and sexual problems (SSRIs and SNRIs),[77;78] as well as dizziness, fatigue and headaches (pregabalin).[79] Less common side effects include palpitations, tachycardia, orthostatic hypotension, and increase in blood pressure (SNRIs).[80;81] Both SSRIs and SNRIs

may result in suicidal thinking and self-harming behaviour in a minority of young people.[82;83] Finally, SSRIs can cause gastrointestinal bleeding, especially if they are administered alongside nonsteroidal anti-inflammatory drugs (NSAIDs).[84] According to the guideline systematic review of side effects associated with pharmacological treatments used in GAD,[19] data on the risk for common, tolerable side effects have not been consistently collected and reported across RCTs; in contrast, discontinuation due to intolerable side effects has been widely reported across trials. Development of intolerable side effects is expected to reduce more significantly the health-related quality of life (HRQoL) of patients with GAD compared with the presence of tolerable side effects.

No studies reporting disutility due to side effects in patients with GAD were identified in the literature. One study examined the effect of the presence of side effects from antidepressants in the HRQoL of patients with depression.[85] In this study, patients with a side effect reported lower utility scores compared with those not experiencing side effects. The observed mean disutility ranged from 0.01 for dry mouth and nausea to 0.12 for nervousness and light-headedness. However, except for light-headedness and dizziness, the reduction in utility caused by side effects did not reach statistical significance.

Based on the above, the economic analysis did not consider the reduction in utility caused by tolerable side effects, but did take into account the ‘disutility’ caused by intolerable side effects. This was assumed to equal 0.12 and to last 2 weeks, as drug

discontinuation due to intolerable side effects was estimated by the GDG to occur usually within 2 weeks from initiation of a particular drug.

Cost data considered in the economic analysis

The perspective of the economic analysis was that of the NHS and PSS, as recommended by NICE.[86] Costs consisted of intervention costs (drug acquisition and GP visit costs) and other health and social care costs incurred by patients with GAD not responding to treatment or relapsing following response. Intervention costs of no pharmacological treatment related to GP visit costs only. All costs were expressed in 2011 prices, uplifted, where necessary, using the Hospital & Community Health Services (HCHS) Pay and Prices Index.[87] Discounting of costs was not necessary since the time horizon of the analysis was shorter than one year.

Drug acquisition costs were taken from UK national sources.[12] For each drug the lowest reported price was selected and used in the analysis; where available, costs of generic forms were considered. The average daily dosage of each drug was determined according to optimal clinical practice (based on the expert opinion of the GDG) and was consistent with the respective average daily dosage reported in the RCTs considered in the economic model. The cost of one month's drug supply before switching to second-line treatment was modelled for patients discontinuing treatment due to intolerable side effects. The ingredient cost of the second-line drug in each arm of the model equalled the average ingredient cost of all drugs except the first-line drug in this particular arm.

The number of GP visits was estimated based on the GDG expert opinion and was the same for first-line and second-line treatment. Patients visited their GP 3 times over the 8 weeks of initial treatment and once during the 6 months of maintenance treatment, and this applied also to patients in the 'no pharmacological treatment' arm of the model; patients discontinuing their first-line treatment due to intolerable side effects were assumed to pay one extra GP visit.

Costs of managing tolerable side effects were not considered separately in the analysis, partly due to inconsistent reporting of side effect rates in the RCTs included in the guideline systematic review of clinical evidence. However, the GDG expressed the view that the majority of tolerable side effects would be discussed during monitoring GP visits and would be unlikely to incur considerable extra costs.

Extra health and social care costs incurred by patients with GAD not responding to treatment or relapsing following response relate to contacts with healthcare professionals such as GPs, psychiatrists, psychologists, mental health nurses and social workers, community care, inpatient and outpatient secondary care. These were estimated based on resource use data reported in a national survey on psychiatric morbidity[22], supported by the GDG expert opinion, and national hospital statistics.[88] Resource use data were combined with appropriate national unit costs[87;89] in order to estimate a total weekly cost incurred by patients with GAD. Details on the data and assumptions used at the estimation of this cost are provided in Supplemental Digital Content 3. Patients not responding to second-line pharmacological treatment and those

not responding to no pharmacological treatment were assumed to incur this health and social care GAD-related cost for the remaining time horizon of the analysis following no response. Patients relapsing were assumed to incur this health and social care GAD-related cost over 3 months out of the 6-month maintenance treatment period that led to relapse.

Table I reports all input parameters utilised in the economic model further to the parameters derived from the two network meta-analyses.

Expert opinion and validation of model structure and assumptions

Advice on issues relating to the model structure regarding natural history and treatment patterns of GAD in the UK as well as expert opinion in areas where evidence was lacking were provided by the members of the GDG, a multi-disciplinary team consisting of health professionals and patient and carer representatives with expertise and experience in the field of GAD. The model structure and input parameters were first agreed with the GDG and subsequently were available (along with the results of analysis) for peer-reviewing by stakeholders over the guideline consultation period. An executable version of the model was also available to stakeholders during this period. Following consultation the final guideline was reviewed by an independent review panel.

Handling uncertainty

In order to take into account the uncertainty around the input parameter point estimates, a probabilistic analysis was undertaken, in which input parameters were assigned

probability distributions.[90] Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Mean costs and QALYs for each treatment option were then calculated by averaging across 10,000 iterations.

In addition, Cost-Effectiveness Acceptability Curves (CEACs) were plotted for each treatment option, demonstrating the probability of each intervention being the most cost-effective among the strategies assessed at various levels of willingness-to-pay per QALY gained.[91] Finally, the cost-effectiveness acceptability frontier (CEAF) was drawn to demonstrate the treatment option with the highest average net monetary benefit (NMB) at each level of willingness-to-pay.[91]

The distributions of the parameters obtained from network meta-analysis (i.e. the probability of discontinuation due to intolerable side effects and the probability of conditional response for each drug) were defined directly from values recorded in 10,000 iterations performed in WinBUGS. The probability of relapse for no pharmacological treatment and utility values were given a beta distribution. The relative risk of relapse of drug treatment versus no treatment was assigned a log-normal distribution. Costs (with the exception of drug acquisition costs) were assigned a gamma distribution, assuming a 30% standard error around the mean values. Table I provides details on the types of distributions assigned to each input parameter (except outputs of network meta-analysis) and the methods employed to define their range.

One-way sensitivity analyses (run with the point estimates rather than the distributions of the input parameters) explored the following scenarios:

- a 70% change in the weekly health and social care cost incurred by patients with GAD not responding to treatment or relapsing following response; this scenario was tested as this cost estimate was based on a number of data extrapolations, assumptions and the GDG expert opinion.
- three extra GP visits following discontinuation of the first line treatment due to intolerable side effects (instead of one extra visit modelled in the base-case analysis).
- a 15% reduction in the responsiveness to the second-line drug (calculated as the average probability of conditional response of all drugs considered in the analysis except the first-line drug in each particular decision node of the model).
- a 15% change in the utility score corresponding to the state of response combined with a 15% change (in the opposite direction) in the utility score corresponding to the state of relapse; the purpose of this scenario was to explore the robustness of the results under potential changes in the scope for utility improvement or deterioration following response to treatment or relapse, respectively.

Results

Results of network meta-analyses

The findings of the two network meta-analyses of data on discontinuation due to side effects and on conditional response are provided in Tables II and III, respectively. Each

table provides the hazard ratios of every drug considered in the economic analysis versus placebo; the probability of every treatment option to result in discontinuation due to intolerable side effects and conditional response, respectively, over 8 weeks of treatment; and the probability of each option being the ‘best’ among available options in either averting discontinuation due to side effects or in achieving conditional response. In both tables, treatment options have been ranked from ‘best’ to ‘worst’ in terms of their ability to minimise discontinuation due to side effects or their ability to lead to conditional response, according to the results of the respective network meta-analyses.

As expected, placebo had the lowest probability of discontinuation due to side effects (mean 0.059 over 8 weeks). All drugs showed a significantly higher hazard of discontinuation versus with placebo, except sertraline. Sertraline had the lowest probability of leading to discontinuation due to side effects among drugs (mean 0.073 over 8 weeks), followed by pregabalin, escitalopram, paroxetine, venlafaxine XL and, finally, duloxetine (mean 0.179 over 8 weeks). The probability of sertraline being the best drug in minimising discontinuation due to side effects reached 0.60.

In terms of conditional response, all drugs showed a significant effect over placebo. Duloxetine had the highest probability of conditional response (mean 0.649 over 8 weeks), followed by sertraline, venlafaxine XL, pregabalin, escitalopram and paroxetine (mean 0.516 over 8 weeks). Placebo had the lowest probability of conditional response among options assessed (mean 0.425 over 8 weeks). The probability of duloxetine

being the best drug in terms of response in people who have not discontinued their drug treatment was approximately 0.38.

Results of economic analysis

Sertraline was the dominant strategy as it was associated with the mean lowest total costs and produced the highest mean number of QALYs among all treatment options assessed (out of the 10,000 iterations of the model). No pharmacological treatment was dominated by all drugs except pregabalin; the latter was more effective than placebo at an extra cost of £2,496 per QALY.

Table IV provides mean costs and QALYs (95% CI) of all treatment options assessed in the economic analysis. The seven options have been ranked from the most to the least effective in terms of the number of QALYs gained. Figure 4 provides the cost effectiveness plane showing the incremental costs and QALYs of all drugs versus paroxetine. Sertraline is in the southeast quadrant of the plane while the 4 remaining drugs are in the northeast quadrant (no treatment is not shown on this graph).

Figure V shows the CEACs generated for each treatment option assessed in the economic model. Sertraline has the highest probability of being the most cost-effective option, at any level of willingness-to-pay per extra QALY gained. At the lower NICE cost effectiveness threshold of £20,000/QALY[92] the probability of sertraline being cost effective is 0.75; the respective probability for escitalopram, which appears to be the second most cost-effective option, is 0.09. The CEAF coincides with the CEAC for

sertraline, meaning that sertraline produces the highest average net monetary benefit at any level of willingness-to-pay.

Results were robust under all scenarios examined in one-way sensitivity analyses: sertraline remained dominant when the health and social care costs incurred by patients not responding to treatment or relapsing following response increased by 70%, when 3 extra GP visits (instead of one) were assumed in the case of discontinuation of first line treatment, when conditional response for the second-line drug was reduced by 15%, and when utility scores for the states of response and relapse were concurrently changed by 15%. Sertraline dominated all options except no treatment when the health and social care costs decreased by 70%; in this case, the ICER of sertraline versus no treatment was £655/QALY, a figure well below the lower NICE cost effectiveness threshold.[92]

Discussion

The findings of our economic analysis suggest that sertraline is likely to be the most cost-effective pharmacological treatment for patients with GAD in the UK at any level of willingness-to-pay, with a probability reaching 75% at the NICE lower cost effectiveness threshold of £20,000/QALY. Results were based on probabilistic analysis and were robust under alternative scenarios examined in one-way sensitivity analysis. The cost-effectiveness of sertraline is attributable to a number of factors: our network meta-analysis showed that sertraline was the best drug in minimising discontinuation due to intolerable side effects, and the second best drug in achieving response in patients not

discontinuing treatment due to side effects; in addition, sertraline currently has the lowest acquisition cost among all drugs assessed in the UK, as it is available in generic form. It must be noted that the probability of cost effectiveness of each treatment option in any probabilistic analysis is determined by the relative cost-effectiveness across the treatment options assessed, as well as the number of options included in the analysis. Therefore, the high probability of cost effectiveness for sertraline does not necessarily indicate the lack of cost effectiveness of the other drugs included in the analysis relative to no treatment (placebo): if sertraline was excluded from the analysis, the probabilities of the remaining options being cost-effective at a willingness-to-pay of £20,000/QALY would be: duloxetine 16.1%; escitalopram 35.8%; paroxetine 26.8%; pregabalin 0.7%; venlafaxine 19.4%; and no pharmacological treatment 1.2%. These results show that in the absence of sertraline no other drug (of those assessed) would demonstrate a clear superiority over the others in terms of cost-effectiveness; nevertheless, selecting 'no pharmacological treatment' instead of one of the remaining drugs for the managemet of patients with GAD would have a probability of being cost-effective as low as 1.2% (at the £20,000/QALY threshold).

Our findings suggest that drug acquisition cost is an important factor in determining the cost effectiveness of pharmacological treatments for GAD. Indeed, if sertraline's acquisition cost equalled that of pregabalin (i.e. the drug with currently the highest acquisition cost), then not only would sertraline not be the dominant option anymore, but its ICER versus escitalopram (currently the next most cost-effective option) would reach £87,000/QALY. On the other hand, if pregabalin's acquisition cost equalled that of

sertraline, pregabalin would dominate all options except sertraline and duloxetine; sertraline would still remain the dominant option, but the low cost of pregabalin would result in an ICER of duloxetine versus pregabline that would exceed £1,000,000/QALY (under current acquisition costs duloxetine was found to dominate pregabalin). It is therefore expected that the relative cost effectiveness of drugs for the treatment of GAD may potentially change in the future, as eventually drugs will become available in generic forms, resulting in a considerable reduction in their acquisition costs.

It must be noted that, despite being ranked as the most cost-effective drug in our analysis, sertraline is currently not licensed for the treatment of GAD in the UK. The drug was considered in our study because available evidence demonstrated its acceptability and clinical effectiveness in the treatment of GAD. In addition, sertraline is widely used in the UK for the treatment of depression and mixed depression and anxiety; it is acknowledged that sertraline is possibly less commonly used in the treatment of GAD, but this is likely partly attributable to the underdiagnosis of GAD in patients presenting with anxiety in primary care.

Clinical effectiveness data utilised in the economic analysis were derived from 39 double-blind RCTs on patients with GAD, identified in a systematic review undertaken for the NICE clinical guideline[19] that was updated for this paper. The overall quality of evidence was rated by producing GRADE profiles which take into account various factors associated with the validity of meta-analytic data,[93] and was judged to be of limited risk of bias. Data from this review were synthesised using network meta-analytic

techniques. This methodology for evidence synthesis enabled us to consider information from both direct and indirect comparisons between treatments, and allowed simultaneous inference on all treatments, without ignoring part of the evidence base and without breaking the rules of randomisation.[20;21] Such methodology for evidence synthesis is being increasingly used in psychiatric research, with recent publications in the areas of anxiety,[94] depression,[95] bipolar disorder,[96;97] and psychosis.[98]

Baldwin et al[94] conducted a network meta-analysis to assess the efficacy and tolerability of nine drugs (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine) in the treatment of GAD. A subanalysis included only drugs licensed for GAD in the UK. According to the study findings, sertraline was the best drug in terms of tolerability (followed by pregabalin, fluoxetine and paroxetine), and fluoxetine was the best drug in terms of response (followed by lorazepam, duloxetine and sertraline). Our network meta-analyses differ from those conducted by Baldwin and colleagues in the following areas:

- Inclusion criteria: our primary objective was to assess the cost-effectiveness of appropriate first-line pharmacological treatments, used in the long-term management of patients with GAD (i.e. beyond 4 weeks), and therefore we considered a more limited choice of drugs in our meta-analyses. Lorazepam is recommended for use up to 2-4 weeks;[12] consequently it was not considered in our economic analysis and the network meta-analyses that informed it. Tiagabine was not included in our analysis as it is neither licensed, nor in wide use for the

treatment of GAD in clinical practice. Regarding fluoxetine, which was not included in our analysis, there was only one relevant study[99] included in the network meta-analysis undertaken by Baldwin and colleagues; this, however, was excluded from our systematic review as it was a secondary analysis of a trial in patients with major depression and concomitant anxiety and was not originally intended to specifically evaluate treatment for GAD. Due to its design, inclusion of this study in the Baldwin et al network meta-analysis has been criticised by Barbui and Cipriani,[100] who also questioned the inconsistency between the results of the Baldwin et al. network meta-analysis and the findings of the original study.

- Outcomes of interest: while Baldwin et al. modelled response based on an intention-to-treat approach (i.e they estimated response rates in all participants in each trial), we considered *conditional* response as the outcome of one of our network meta-analyses, i.e. we estimated response in patients not discontinuing treatment due to intolerable side effects. This was dictated by the structure of the economic model and was essential in order to populate the model without underestimating response rates in patients who continued treatment.
- Method of analysis: Baldwin et al compared every pair of treatments by estimating the odds ratio of each outcome. However, this method cannot give consistent results when trials have very different follow-up times,[25] because odds ratios change over time; in contrast, in order to take into account the different time horizons of the trials (range 4 to 28 weeks) we compared every pair of treatments by estimating the hazard ratio of each outcome, assuming constant hazard of each

outcome in every study over time, to account for the different follow-up times of the studies included in the meta-analyses.

Nevertheless, after excluding the drugs considered by Baldwin and colleagues but not by our network meta-analyses, the rankings of the first 2 drugs are the same in the two studies: in both studies sertraline is ranked first in terms of tolerability followed by pregabalin; and duloxetine is ranked first in terms of response, followed by sertraline.

In another network meta-analysis comparing relative efficacy and tolerability of 12 new-generation antidepressants for patients with unipolar major depression, Cipriani and colleagues reported that sertraline, venlafaxine, escitalopram and mirtazapine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine, while escitalopram and sertraline were ranked best in terms of acceptability, leading to significantly fewer discontinuations compared with duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.[95] The authors concluded that sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it had the most favourable balance between benefits, acceptability, and acquisition cost. Although the study assessed efficacy and tolerability of antidepressants in a different study population than ours (patients with unipolar major depression versus patients with GAD), the authors' conclusions are fully in line with our findings.

Few economic analyses have explored the relative cost-effectiveness between drugs in the treatment of GAD.[14-17] All studies used economic modelling techniques in order to make pair-wise comparisons of a limited number of drugs, each deriving efficacy data from single RCTs (rather systematic reviews and meta-analyses). None of the studies compared more than two pharmacological treatment options. Two studies assessed the cost-effectiveness of escitalopram versus paroxetine in Canada[14] and in the UK.[15]. In Canada, escitalopram was reported to be more effective than paroxetine at an extra cost of $2,362 per symptom-free year from the perspective of the Ministry of Health (in 2005 Canadian dollars), while it dominated paroxetine from a societal perspective;[14] in the UK, escitalopram was both more effective and overall less costly than paroxetine from both healthcare provider (UK NHS) and societal perspectives.[15] Another study examined the relative cost-effectiveness between venlafaxine XL and diazepam in the UK;[16] the authors concluded that venlafaxine XL was more effective at an extra cost of £381 per successfully treated patient with GAD from the perspective of the UK NHS (2001 prices). Finally, Vera-Llonch et al.[17] evaluated the cost effectiveness of pregabalin relative to venlafaxine XL from the Spanish healthcare perspective; pregabalin was shown to be more costly and more effective than venlafaxine XL, with an ICER of €23,909/QALY (2007 prices). It is apparent from the above findings that previous economic evidence on pharmacological treatments in the area of GAD is very sparse, limited to a very small number of treatment options, and therefore insufficient for making any inference on the relative cost effectiveness of the full range of available pharmacological treatments for the management of GAD. In contrast, our economic analysis considered 6 drugs appropriate for first-line, long-term pharmacological

treatment of patients with GAD, and utilised clinical data from a systematic review of the literature, synthesised using network meta-analytic techniques, which are essential for model-based economic studies assessing more than two competing interventions. The results of our economic analysis are expected to be generalizable to settings where the funding and structure of healthcare services as well as the care pathways relating to the clinical management of GAD are similar to those in the UK.

One limitation of our economic analysis was the fact that it did not take into account the reduction in HRQoL and the costs associated with the management of tolerable side effects that do not lead to treatment discontinuation, due to inconsistent reporting of side effects across trials included in the systematic review and to lack of evidence on the reduction in HRQoL caused by the presence of side effects from drugs in patients with GAD. Nevertheless, existing evidence suggests that the reduction in HRQoL associated with the presence of side effects from antidepressants is largely insignificant in patients with major depression;[85] regarding costs of managing side effects, these were not considered to be substantial, as most common side effects from medication are expected to be managed during GP monitoring visits, which have already been considered in the analysis. On the other hand, our economic model did consider the impact of the development of intolerable side effects, which lead to treatment discontinuation, on costs and HRQoL of patients with GAD.

Another limitation of our model structure is that in order to estimate clinical and cost parameters for the second-line pharmacological treatment we used the average

probabilities of discontinuation and conditional response and the avergage acquisition cost, respectively, of all drugs considered in the analysis, except the first-line option for that arm of the model. Ideally, we should have used weighted average figures, according to actual utilisation of these drugs in the treatment of patients with GAD in the UK. However, accurate data on actual drug utilisation patterns in patients with GAD are not available, due to the underdiagnosis of GAD in patients presenting with anxiety in primary care.

Efficacy data on sertraline were derived from a small number of published studies relative to other drugs (two placebo-controlled trials, which, nevertheless, included 706 participants). We identified a further placebo-controlled trial on sertraline sponsored by the Department of Veteran Affairs USA (clinicaltrials.gov ID: NCT00701675). However, we were unable to obtain data from this trial. Inclusion of these data in the analyses might have impacted on our conclusions. It must be noted that the studies considered in our network meta-analyses were largely sponsored by the drug industry. The extent of selective publishing by the industry in the area of GAD is not known, but such tactics have led to an overestimation of the benefits and an underestimation of the risks associated with the SSRIs in other disease areas, such as the treatment of depression in children[101] and in adults,[102] and one needs to bear this in mind when interpreting the findings of our network meta-analyses as well as the results of other similar work published in this field.

Our analysis adopted the perspective of the NHS and PSS, as our objective was to explore resource use implications within the healthcare and personal social services sector. Therefore, productivity losses in terms of absenteeism from work were not considered in our model. However, it is anticipated that higher rates of adherence and response to treatment, besides resulting in a reduction in healthcare resource use, are most likely to lead to improved functioning, and this, in turn, is expected to lead to a reduction in days of sick leave and reduced productivity and decrease in total productivity losses. This speculation is consistent with the findings of 2 of the economic evaluations that have been published in the area of GAD that adopted both healthcare and societal perspectives: both studies demonstrated that drugs shown to be cost-effective under the healthcare perspective were associated with more remarkable favourable results when a societal perspective was adopted.[14;15] Thus, consideration of productivity losses in our economic analysis would most probably strengthen the cost-effectiveness findings in favour of sertraline, which was the drug with the highest number of responders at 8 weeks, and the highest number of patients improving without a relapse at endpoint of analysis.

Based on the findings of our economic analysis, the NICE clinical guideline on GAD[19] recommended that clinical practitioners consider offering sertraline as first-line option in patients with GAD choosing drug treatment, bearing in mind that sertraline did not have UK marketing authorisation for GAD at the time of publication of guidance. However, because of consistent evidence of a greater risk of side effects and treatment discontinuation associated with drugs compared with placebo, the guideline concluded

that low-intensity psychological interventions should be considered first in the treatment of patients presenting with GAD in primary care, while pharmacological treatments should only be routinely offered to patients who have not benefitted from low intensity psychological interventions and have a preference to try medication rather than a high intensity psychological therapy.[19]

Conclusion

The economic analysis presented in this paper suggests that sertraline is likely to be the most cost-effective drug in the treatment of GAD and therefore should be offered to patients with GAD where pharmacological treatment is indicated.

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Table I. Input parameters utilised in the economic model (in addition to parameters obtained from network meta-analysis)

Input parameter	Deterministic value	Probabilistic distribution	Source of data - comments
Probability of relapse – no treatment	0.4740	**Beta distribution** α=529; β=587	Pooled data from placebo arms of 6 RCTs on relapse prevention in GAD included in the updated guideline systematic review[68-73]
Relative risk of relapse – drugs versus placebo	0.31	**Log-norm distribution** 95% CIs: 0.25 to 0.38	Updated guideline meta-analysis of 4 RCTs assessing SSRIs or SNRIs for relapse prevention in GAD[68-71]
Utilities			
Response	0.760	**Beta distribution** α=177.84; β=56.16	Estimated using method of moments from data reported in [74]
Non-response	0.630	α=24.57; β=14.43	
Relapse	0.730	α=51.83; β=19.17	
No relapse following response	0.790	α=97.96; β=26.04	
Disutility due to intolerable side effects	-0.120	α=8.40; β=61.60	Estimated using method of moments from data reported in [85]
Drug acquisition costs	**(8-week cost)**		

Duloxetine – 60mg/day Escitalopram – 10 mg/day Paroxetine – 20 mg/day Pregabalin – 300 mg/day in two doses Sertraline – 100 mg/day Venlafaxine XL – 75 mg/day	£55.44 £29.82 £4.20 £128.80 £3.60 £44.16	**No distribution assigned**	BNF 63 [12]
GP visit costs (common in all treatment options) Initial 8-week treatment Maintenance 6-month treatment Discontinuation of treatment	 £108 £36 £36	**Gamma distribution** SE: 30% of mean value (assumption)	Assuming 3 visits over the 8 weeks of initial treatment, 1 visit during the 6 months of maintenance treatment and 1 extra visit in case of discontinuation (GDG expert opinion); combined with UK national unit costs[87]
Weekly health and social care cost incurred by people with GAD	£19.32	**Gamma distribution** SE: 30% of mean value (assumption)	Based on resource use data from a UK national psychiatric morbidity survey[22] and the GDG expert opinion, combined with UK national unit costs;[87;89] average length of inpatient stay for people with GAD based on UK national sources.[88] See Supplemental Digital Content 3 for more details.

CI = confidence intervals; SE = standard error

Table II. Findings of network meta-analysis: pharmacological treatment discontinuation due to side effects

Treatment options have been ranked from 'best' to 'worst' in terms of limiting discontinuation due to side effects

Drug	HR versus placebo (95% CrI)	Pr of discontinuation due to side effects at 8 weeks (95% CrI)	Pr that drug is best in averting discontinuation due to side effects (Pr after excluding placebo)
Placebo		0.059 (0.013, 0.163)	0.532 (NA)
Sertraline	1.23 (0.57, 2.42)	0.073 (0.012, 0.237)	0.358 (0.595)
Pregabalin	1.48 (1.06, 2.03)	0.087 (0.017, 0.252)	0.059 (0.225)
Escitalopram	1.62 (1.07, 2.31)	0.095 (0.018, 0.282)	0.044 (0.151)
Paroxetine	2.40 (1.70, 3.35)	0.135 (0.028, 0.384)	0.004 (0.016)
Venlafaxine-XL	2.56 (1.96, 3.33)	0.144 (0.030, 0.404)	0.002 (0.010)
Duloxetine	3.34 (2.24, 4.92)	0.179 (0.038, 0.489)	0.001 (0.003)

Note: Pr = probability; CrI = credible intervals; HR = hazard ratio

Table III. Findings of network meta-analysis: conditional response to pharmacological treatment

Treatment options have been ranked from 'best' to 'worst' in terms of achieving response in patients not discontinuing treatment due to intolerable side effects

Drug	HR versus placebo (95% CrI)	Pr of conditional response at 8 weeks (95% CrI)	Pr that drug is best in achieving conditional response
Duloxetine	1.97 (1.58, 2.41)	0.649 (0.362, 0.920)	0.381
Sertraline	1.85 (1.30, 2.54)	0.625 (0.326, 0.910)	0.272
Venlafaxine-XL	1.78 (1.49, 2.10)	0.614 (0.335, 0.896)	0.165
Pregabalin	1.65 (1.36, 1.97)	0.588 (0.314, 0.874)	0.090
Escitalopram	1.60 (1.25, 2.02)	0.578 (0.299, 0.872)	0.077
Paroxetine	1.33 (1.06, 1.65)	0.516 (0.260, 0.815)	0.015
Placebo		0.425 (0.222, 0.686)	0.000

Note: Pr = probability; CrI = credible intervals; HR = hazard ratio

Conditional response = response in patients who have not discontinued the drug due to side effects

Table IV. Costs and QALYs per patient with GAD for each pharmacological treatment option assessed in the economic analysis (results based on 10,000 iterations of the economic model)

Treatment option	Total QALYs (95% CI)	Total costs (95% CI)
Sertraline	0.588 (0.531 to 0.633)	£390 (£233 to £606)
Duloxetine	0.586 (0.528 to 0.632)	£526 (£399 to £717)
Pregabalin	0.586 (0.527 to 0.633)	£696 (£579 to £851)
Venlafaxine XL	0.586 (0.527 to 0.632)	£502 (£369 to £694)
Escitalopram	0.586 (0.526 to 0.632)	£470 (£329 to £668)
Paroxetine	0.582 (0.521 to 0.631)	£440 (£274 to £658)
No treatment	0.547 (0.461 to 0.624)	£599 (£343 to £943)