A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive–compulsive disorder in children/adolescents and adults

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Scientific summary

Interventions for obsessive–compulsive disorder

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Scientific summary

Background

Obsessive–compulsive disorder (OCD) is the fourth most common mental disorder in the UK and ranks 10th in the World Health Organization's leading causes of disability worldwide. The course of the disorder is usually chronic and may lead to considerable disability without treatment. Despite its prevalence, the disorder is under-recognised and undertreated. The total costs of OCD have been estimated, in the USA, to be US$8.4B in 1990, which is 5.7% of the estimated US$147.8B cost of all mental illness and 18.0% of the costs of all anxiety disorders. Specific information on indirect and total costs of OCD and the cost-effectiveness of alternative treatments is limited in the UK and elsewhere.

Objectives

The main aim of this review was to determine the clinical effectiveness, acceptability and cost-effectiveness of pharmacological and psychological interventions for the treatment of OCD.

More specifically, the aims were the following:

1. to undertake a systematic review of the clinical effectiveness and acceptability of pharmacological and psychological interventions for the treatment of OCD in all age groups
2. to perform a network meta-analysis (NMA) of all randomised evidence (both direct and indirect), with the aim to rank all treatments in terms of efficacy and acceptability
3. to develop a probabilistic economic model of alternative treatments (pharmacological and psychological) for the management of OCD in order to evaluate the relative cost-effectiveness of these treatments.

Methods

Search methods and inclusion criteria

We searched the Cochrane Collaboration Depression, Anxiety and Neurosis Group Controlled Trials Registers from inception to 31 December 2014. Reports of trials for inclusion in the Group's registers are collated from routine searches of MEDLINE, EMBASE and PsycINFO, the Cochrane Central Register of Controlled Trials and review-specific searches of additional databases. A systematic review of economic evaluations of pharmacological and psychological interventions in OCD was also conducted using standard methods for evidence synthesis.

Only randomised controlled trials were eligible for inclusion. Studies that focused exclusively on treatment-refractory patients were not included. Active pharmacological interventions included any antidepressant medication with some serotonergic properties. Active psychological interventions included behavioural therapy (BT) (exposure and response prevention), cognitive–behavioural therapy (CBT) and cognitive therapy (CT). We used a standard methodology for data extraction.

Outcomes

For the clinical effectiveness analysis, we used the severity of OCD symptoms at the end of study or the change in symptoms from baseline as measured by the Yale–Brown Obsessive–Compulsive Scale in adults or the Children's Yale–Brown Obsessive–Compulsive Scale in children and adolescents. For the acceptability analysis, we used the total dropout rates. For the cost-effectiveness analysis, the model evaluated the cost-effectiveness of pharmacological interventions, psychological interventions and combinations of both from a NHS perspective.

Data synthesis

Pairwise analyses and NMAs were conducted in a Bayesian framework using OpenBUGS version 3.2.3 (members of OpenBUGS Project Management Group; see www.openbugs.net). Pairwise meta-analyses were conducted in a single model, assuming independent treatment effects and a shared heterogeneity parameter. In the NMA program code, we incorporated an additional class hierarchy, such that interventions with a similar mechanism of action were grouped together in a class in which pooled effects might be assumed to be 'similar'. Random-effects models were used, accounting for the correlation between trial-specific effects in multiarm studies. Vague priors were used for all parameters. We report the relative effectiveness of each treatment compared with every other treatment, as well as the probability that each treatment is the most effective on each outcome.

For the cost-effectiveness analysis, we developed a decision-analytics model to evaluate the cost-effectiveness [cost per quality-adjusted life-year (QALY) gained] of pharmacotherapies, psychological interventions and combinations of both from a NHS perspective over a 5-year time frame. All active interventions that were included in the NMA were compared in the model. We elected to evaluate selective serotonin reuptake inhibitors (SSRIs) at the class level in the cost-effectiveness analysis. In total, the cost-effectiveness of eight interventions in the adult model and five interventions in the children/adolescent model were compared. The model comprises a decision tree covering the initial response to treatment at 12 weeks and a Markov model to simulate the course, costs and outcomes (utilities) of OCD from 12 weeks to 5 years. The model draws on evidence from the NMA to inform the probability of response (full, partial and no response) and dropout during the initial 12 weeks. Initial pharmacological and psychological therapy costs are estimated based on data on mean daily dose and total number of therapist contact hours provided in the trials identified by the systematic review. Longer-term mortality, symptom course and NHS costs and utilities were estimated based on epidemiological and economic studies identified through reviews of the literature. The model uses probabilistic analysis to quantify the stochastic uncertainty around estimates of cost-effectiveness. The importance of parameter and structural uncertainty is also tested through a series of deterministic sensitivity analyses. The cost-effectiveness of each intervention is summarised using the net benefit statistic at thresholds of £20,000 and £30,000 per QALY gained. The probability that each intervention is the most cost-effective at a range of willingness-to-pay thresholds (£0–50,000 per QALY) is summarised using cost-effectiveness acceptability curves.

Results

Systematic review

A total of 1083 abstracts were screened and 86 studies reported in 85 papers were included in the review (64 in adults and 22 in children and adolescents), involving 8611 randomised patients (7306 adults and 1305 children and adolescents). In the total sample, 23 different interventions were tested in 194 arms. In adults, interventions with more studies were clomipramine ($n = 17$), fluvoxamine ($n = 16$) and BT ($n = 15$), whereas in children and adolescents CBT ($n = 9$), fluoxetine ($n = 4$), clomipramine ($n = 4$) and sertraline ($n = 4$) were the most frequently studied treatments. Regarding quality, the majority of the studies did not describe adequately the random sequence generation and the allocation sequence concealment. In the adult subset, $< 50\%$ of the trials reported results based on the intention-to-treat principle. Studies of clomipramine and studies of psychological interventions only were more likely to report completers' analysis. In addition, several studies with psychological arms have used waitlist controls and, therefore, these comparisons were unblinded from the patient's perspective.

Network meta-analysis

Clinical effectiveness in adults

A total of 54 studies were included in this analysis, involving 6652 randomised patients. All active interventions, apart from venlafaxine and hypericum, had a greater effect on symptom reduction than drug placebo. Regarding the pharmacological interventions, SSRIs as a class had greater effects than placebo [class effect mean difference (MD) –3.49, 95% credible interval (CrI) –5.12 to –1.81] with small differences between them. There was a trend for clomipramine to have a greater effect than SSRIs, but the 95% CrI included the null value. Regarding the psychological interventions, all active psychotherapies had greater effects than drug placebo; BT and CT had the largest effects and small differences were observed between them (class effect MD –1.12, 95% CrI –1.95 to 4.19 for the comparison between BT and CT). Regarding the comparison between psychological interventions and psychological placebo, both BT and CT had greater effects (MD –10.33, 95% CrI –13.38 to –7.29 and MD –9.21, 95% CrI –13.10 to –5.34, respectively) but the effect of CBT was not significantly different from psychological placebo (MD –1.22, 95% CrI –5.54 to 3.03). Regarding the comparison between psychological and pharmacological interventions, both BT and CT had greater effects than SSRIs as a class or clomipramine. The difference with CBT was smaller and the 95% CrI included the null value. Combinations of medications and psychotherapy showed large effects compared with drug placebo, with small differences between the effects of psychotherapy as monotherapy. In terms of ranking, BT and CT were the two best treatments, followed by combinations of drug and psychotherapy, CBT and clomipramine. Sensitivity analyses for incomplete outcome data showed that the effect of clomipramine and CT may have been overestimated, because most of the studies reported completers' analyses.

Clinical effectiveness in children and adolescents

Seventeen studies were included in the analysis, involving 991 randomised patients. CBT and BT had greater effects than drug placebo. Compared with psychological placebo, both therapies, and especially CBT, showed a non-significant trend for a greater effect. SSRIs as a class showed a non-significant trend for a greater effect compared with drug placebo. Individual SSRIs, however, reached marginal statistical significance. Compared with SSRIs as a class, both psychological therapies (BT and CBT) showed a non-significant trend for a greater effect. Similar results were found for clomipramine. It should be noted that a limitation of the CBT trials is that, in four of the seven included studies, the control group was the waitlist (unblinded comparison), and in such studies the effect of CBT was larger than in CBT trials that did not use the waitlist as the control. The combination of sertraline with CBT was associated with the largest effect compared with drug placebo, but compared with CBT as monotherapy, the combination had similar effects. These results should be interpreted with caution owing to the use of the waitlist control in CBT trials. Sensitivity analyses gave results with similar trends.

Acceptability

All active interventions except clomipramine showed good tolerability in adults compared with placebo. In children and adolescents, BT showed a non-significant trend towards worse tolerability, but this finding was based on two small trials. CBT in children and adolescents showed very good tolerability, and the combination of sertraline with CBT was ranked first in acceptability.

Cost-effectiveness analysis

The selection of the most cost-effective therapy for adults or children and adolescents with OCD is not clear-cut. In both populations, the most effective therapies were also among the more expensive therapies; there is a trade-off between the higher upfront costs of psychological therapies and the potential for them to improve outcomes and reduce long-term costs of care. In the primary economic evaluation in adults, psychological therapies, specifically CT and BT, had the highest probability of being most cost-effective at the conventional National Institute for Health and Care Excellence (NICE) thresholds (£20,000–30,000 per QALY) and above. CBT had a low probability of being cost-effective in adults at all cost-effectiveness thresholds. This was predominantly because of the substantially lower estimated effect size of CBT compared with CT and BT and the higher intensity and, therefore, cost of CBT evaluated in randomised

controlled trials. At lower willingness-to-pay thresholds (< £10,000 per QALY), pharmacotherapy had a relatively high probability of being cost-effective.

There is substantially less trial evidence in children and adolescents. Of the five interventions compared, SSRIs had the highest probability of being most cost-effective at lower willingness-to-pay thresholds (< £15,000 per QALY). At the conventional NICE thresholds (£20,000–30,000 per QALY) and above, CBT or CBT combined with a SSRI was more likely to be cost-effective.

Discussion

These results confirm previously published guidelines, based on direct evidence only, that a range of pharmacological and psychological interventions is effective in the short-term management of OCD. One of the advantages of the present analysis is that the use of a NMA allows the simultaneous comparison of multiple competing treatments in a single statistical model, even if treatments have not been directly compared. As there was no imbalance in the presence of potential effect modifiers, we can assume that there was no inconsistency between the direct and indirect sources of evidence.

The results of the NMA show that all active psychotherapies, in particular BT in adults and CBT in children and adolescents, had greater effects than drug placebo. CT in adults also showed a large effect compared with BT, but it is worth noting that this therapy had very few direct links with other interventions apart from BT, and the evidence is mainly based on completers' analyses. CBT in adults showed a small effect compared with the other two psychotherapies and its effect was not statistically significantly different from that of psychological placebo. In children and adolescents, CBT had a large effect, but a limitation is that most of the trials have used a waitlist control, and in these studies the effect of CBT was higher than in studies that used other control treatments.

Selective serotonin reuptake inhibitors had very good tolerability, but their effect in adults, although larger than that of drug placebo, was worse than that of psychotherapies. It should be pointed out that the majority of the psychotherapy trials included patients with stable medication use (mainly SSRIs) but who met diagnostic criteria for OCD and the severity of whose disease was above the cut-off point for inclusion in the study. It is likely that this may have influenced the results in favour of psychotherapies. In addition, there is evidence that longer-term treatment with medications may have beneficial effects over and above the effects reported in the short term. It should also be noted that several psychotherapy trials have used waitlists as their control and, therefore, the patients receiving the active intervention were not blinded to treatment. In children and adolescents, the effect of SSRIs as a class was non-significant, although individual drugs (sertraline and fluoxetine) were marginally more effective than drug placebo. The combination, however, of sertraline with CBT had the largest effect, which was comparable to the combination of drug placebo and CBT.

In adults, clomipramine showed a non-significant trend for superiority over SSRIs, but the exclusion of studies with completers' analysis attenuated this difference. However, clomipramine was associated with worse tolerability. Therefore, the results of the present analysis support the recommendation for the use of clomipramine as a second-line pharmacological treatment.

Combinations of medications with psychotherapies showed large effects that are comparable to psychotherapy monotherapies (although, as mentioned previously, most of the included patients in 'monotherapy' arms were also taking stable doses of SSRIs or clomipramine). Tolerability of the combinations was generally good and was excellent in children and adolescents.

The results of the economic evaluation reflect considerable uncertainty from many different sources. Results are sensitive to assumptions about the sustainability of treatment effects beyond the initial treatment period and exclusion of trials at high risk of bias.

Conclusions

The results of this review support a range of effective options, both pharmacological and psychological, for the management of OCD in all age groups. Regarding the relative effectiveness, our review highlighted the great uncertainty surrounding the published randomised evidence. Although specific psychological interventions were found to have larger effects than medications, there are important methodological limitations that need to be taken into account in future research before a final decision can be made. Regarding cost-effectiveness, current recommendations are not inconsistent with the evidence synthesised in this report, but, depending on the assumptions, economic implications between interventions may arise. Future randomised controlled trials should improve methods of investigating the relative effectiveness of pharmacological versus psychological interventions or combinations of them and take into account issues of blinding in psychotherapy trials.

Study registration

This study is registered as PROSPERO CRD42012002441.

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