Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation

SJ Edwards,* V Hamilton, L Nherera and N Trevor

BMJ Technology Assessment Group (BMJ-TAG), London, UK

*Corresponding author

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Scientific summary

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Scientific summary

Background

Patients with treatment-resistant depression (TRD) are those with major depressive disorder (MDD) that has not responded adequately to treatment. However, there is much uncertainty regarding what constitutes the definition of TRD and whether or not, for example, a patient with a failure to respond to two antidepressants from the same class could be defined as treatment resistant. The focus of this review is patients with unipolar TRD and, for the purposes of this report, TRD has been defined as a failure to respond to two or more antidepressants in the current episode of depression.

No UK-specific data on the incidence or prevalence of TRD are available in the literature. However, it is understood that up to two-thirds of patients diagnosed with MDD will have a suboptimal response to first-line treatment with antidepressant drugs. The World Federation of Societies of Biological Psychiatry guidelines for biological treatment of unipolar depressive disorders state that 'as many as 50% of non-responders to a first antidepressant trial also fail to respond to a second, different course of treatment'.

There are several strategies available for the treatment of patients with TRD. These strategies include pharmacological, non-pharmacological, and psychological and psychosocial interventions. Pharmacological treatment options include switching to a different antidepressant, the addition of another antidepressant of a different class, or use of an augmenting agent, such as anticonvulsant drugs, lithium or atypical antipsychotic drugs (AAPs).

This report contains a health technology assessment of lithium and AAPs used as augmentation therapies in the management of patients with TRD who are already taking selective serotonin reuptake inhibitor (SSRI) antidepressant therapy.

Objectives

The objective of the project was to estimate the clinical effectiveness and cost-effectiveness of augmentation of SSRI antidepressant therapy with either lithium or an AAP in the management of people with unipolar TRD.

The project was split into four distinct pieces of work:

- systematic review of clinical effectiveness of interventions
- systematic review of cost-effectiveness of interventions
- systematic review of quality-of-life (QoL) studies in depression
- de novo economic model.

Methods

Search methods

A systematic review of the literature was carried out to identify potentially relevant randomised controlled trials (RCTs) comparing augmentation of SSRI antidepressant therapy with either lithium or an AAP in the management of people with unipolar TRD. Databases searched were EMBASE, MEDLINE, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the registries of the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group were searched. The NHS Economic Evaluation

Database (NHS EED) was also searched for the economic evaluation studies. All searches were performed from the date of database inception to August 2011. Further data were obtained from manufacturers. Inclusion decisions, quality assessment and data extraction were undertaken independently by two reviewers according to predefined criteria.

Clinical effectiveness

Standard pairwise meta-analysis was conducted using a fixed-effects model as the primary analysis. Mixed-treatment comparisons (MTCs) were conducted using a fixed- and random-effects model, with the best fitting most appropriate model chosen for the reporting of results. The systematic review was registered on PROSPERO (CRD42011001464).

Cost-effectiveness

A de novo mathematical model was developed to synthesise the available data on costs and clinical outcomes from the UK NHS perspective. The model adopted a 1-year time horizon, consisting of 8 weeks of acute treatment (captured by a decision tree) and 10 months of maintenance treatment (captured by a Markov model). The primary outcome of interest was the cost per quality-adjusted life-year (QALY) gained. The model required data on the outcomes of remission, response and discontinuation. Acute efficacy data used in the model were derived from the MTC carried out as part of this review. As a result of a paucity of clinical effectiveness data, a novel sampling approach was used to generate the probabilities required for the economic model. The approach involved sampling the treatment effect [change in MADRS (Montgomery–Åsberg Depression Rating Scale) score from baseline] of each augmentation strategy (from a distribution of possible effects) and calculating the proportion of patients (in a cohort of 1000 for each treatment arm) that would achieve remission or response during the acute treatment phase. The model assumed that outcomes in the maintenance phase were treatment independent.

Results

Clinical effectiveness

Twelve RCTs were identified in the review of clinical effectiveness data. Ten RCTs considered SSRI + AAP compared with SSRI + placebo/no treatment. Of the remaining two RCTs, one was a comparison of SSRI or serotonin–norepinephrine reuptake inhibitor (SNRI) + AAP with SSRI or SNRI + lithium and the final RCT compared SSRI + lithium with SSRI + placebo. Six of the 10 SSRI + AAP trials were included in the primary analysis; the remaining four RCTs were included in a class-based sensitivity analysis. Of the trials considering lithium augmentation as a comparator, only one was included in the primary analysis. All six trials considering augmentation with an AAP included in the primary analysis evaluated fluoxetine (SSRI) + olanzapine (AAP). Furthermore, the lithium trial included in the primary analysis used fluoxetine as the background SSRI in both the comparator group and lithium augmentation group.

Results for selective serotonin reuptake inhibitor plus atypical antipsychotic compared with selective serotonin reuptake inhibitor alone (pairwise comparison)

Five RCTs reported response based on the MADRS and the remaining RCT used the Hamilton Depression Rating Scale. The results of the meta-analysis (fixed effects) demonstrated a statistically significant benefit for fluoxetine + olanzapine over fluoxetine alone [odds ratio (OR) 1.48; 95% confidence interval (CI) 1.13 to 1.94] with a moderate level of statistical heterogeneity ($I^2 = 53\%$; $p = 0.07$).

Five RCTs reported the outcome of remission. Fixed-effects meta-analysis demonstrated a statistically significant increase in remissions in patients treated with olanzapine + fluoxetine compared with fluoxetine alone (OR 1.77; 95% CI 1.27 to 2.47) with no statistical heterogeneity ($I^2 = 0\%$; $p = 0.75$). Data on relapse rates were not available for analysis.

Four RCTs reported least square mean difference (MD) from baseline in MADRS score at study end point. Fixed-effects meta-analysis resulted in a statistically significant MD of –2.04 (95% CI –3.25 to –0.82) in favour of fluoxetine + olanzapine. However, there was a high level of heterogeneity that was statistically significant ($I^2 = 73\%$; $p = 0.01$).

Fixed-effects meta-analysis of five trials found that olanzapine augmentation therapy was associated with a non-statistically significant increase in discontinuations (OR 1.25; 95% CI 0.91 to 1.71) with no statistical heterogeneity ($I^2 = 0\%$; $p = 0.51$).

Selective serotonin reuptake inhibitor plus lithium compared with selective serotonin reuptake inhibitor plus placebo response (pairwise comparison)

The single trial comparing fluoxetine + lithium with fluoxetine alone used two definitions of response, one prespecified primary analysis and one post hoc analysis. Results of the primary and post hoc analyses for response data indicated a non-significant trend in favour of lithium augmentation compared with SSRI alone (OR 1.48; 95% CI 0.37 to 5.95 and OR 3.85; 95% CI 0.80 to 18.62, respectively). Data on remission or relapse rates were not available.

The MD in change in MADRS score from baseline between fluoxetine + lithium compared with fluoxetine alone was –3.79 (95% CI –11.25 to 3.67) – a non-significant improvement from baseline score with fluoxetine + lithium compared with fluoxetine alone.

Data on all-cause withdrawals demonstrated fewer withdrawals with a lithium augmentation strategy than with fluoxetine alone, although this difference was statistically non-significant (OR 0.68; 95% CI 0.15 to 3.16).

Mixed-treatment comparison (selective serotonin reuptake inhibitor plus atypical antipsychotic compared with selective serotonin reuptake inhibitor plus lithium)

Seven RCTs were included in the MTC: six for SSRI + AAP compared with SSRI alone and one RCT for SSRI + lithium compared with SSRI alone. Two separate analyses for the outcome of response were conducted because the trial informing the comparison with lithium reported response using two criteria. Analyses of response (random-effects model) using the lithium primary analysis and the lithium post hoc analysis data showed a non-significant trend in favour of treatment with lithium [OR 1.29; 95% credible interval (CrI) 0.11 to 5.32 and OR 4.15; 95% CrI 0.25 to 20.34, respectively].

Five trials were included in the analysis for mean change in MADRS (four RCTs were AAPs and one was a lithium RCT). The random-effects model resulted in a weighted MD of –1.47 (95% CrI –9.10 to 6.41) for the mean change in MADRS score from baseline for fluoxetine + lithium compared with fluoxetine + olanzapine, which suggests a statistically non-significant trend in favour of lithium augmentation. However, the wide 95% CrI indicates a high level of uncertainty in this estimate of treatment effect and so the results should be interpreted with caution.

Six trials reported data on all-cause withdrawals. The fixed-effects model results suggested a statistically non-significant trend in favour of augmentation with lithium (OR 0.74; 95% CrI 0.10 to 2.66) compared with augmenting with AAP.

Various sensitivity analyses were carried out, including analyses assuming class effects of SSRIs and AAPs, analysis of RCTs in which patients had experienced two or more failures to antidepressants in their current episode, and analysis of RCTs reporting response based on MADRS score. Results of most sensitivity analysis were consistent with the results of the primary analysis. However, the result of the sensitivity analysis assuming a class effect for SSRIs and AAPs for the outcome of mean change in MADRS differed from the primary analysis, identifying a statistically non-significant trend in favour of treatment with SSRI + AAP [MD 1.27; 95% CrI –1.88 to 4.68 (random-effects model)].

Cost-effectiveness

The systematic literature review identified four economic evaluations in the management of TRD and five studies that reported utility values for different levels of depression severity and treatment response. Of the economic evaluations, none directly addressed the review question but all were used to inform the modelling methods. Of the health-state utility values studies, one was used in the QALY calculations of the de novo model.

The monthly cost of the commonly prescribed SSRIs and AAPs varied substantially, whereas the costs of monitoring were modest. The annual cost per patient treated with SSRI + lithium was estimated to be £4739 compared with £5644 for those treated with SSRI + AAP. The difference in cost between the two augmentation strategies is around £905 per person per year, in favour of augmentation with lithium (lithium augmentation is cheaper) and translates to savings of £75 per person per month.

The results of the de novo modelling indicate that augmentation of SSRI therapy with an AAP is dominated by augmentation of an SSRI with lithium. The difference in costs is modest (cost savings £905 per person per year) and the difference in QALYs is estimated to be 0.03 QALYs. It appears there is no uncertainty about the dominance result, as lithium augmentation provided more benefits than AAP augmentation in all probabilistic runs. One-way sensitivity analysis showed that changes in costs had a minimal impact on the overall results, whereas changes in acute efficacy or discontinuation could potentially reverse the direction of the cost-effectiveness results. For example, assuming a low level of acute response (i.e. using the upper CrI) for the treatment effect of lithium (vs. SSRI alone; MD – 12.58, 95% CrI – 33.0 to 7.84) resulted in AAP augmentation having incremental cost-effectiveness ratios of < £20,000/QALY compared with lithium augmentation, as opposed to the base case in which lithium dominates. A similar result was observed when a high level of acute response for AAP was assumed (i.e. using the lower CrI) for AAP treatment effect (vs. SSRI alone; MD – 11.22, 95% CrI – 30.13 to 7.69). However, lithium remained dominant in most of the sensitivity analyses performed.

Discussion

The major weakness of this analysis is the lack of head-to-head data on the effectiveness of the comparison of SSRI + AAP with SSRI + lithium in patients with TRD. The MTC results demonstrate a non-significant benefit of augmenting with lithium compared with augmenting with AAP for most of the outcomes assessed. These results should be interpreted with caution, as the definitions of response and characteristics of patients included in the lithium RCTs differed from those used in the AAP RCTs. The inclusion of slightly different populations and definition of response may bias the results in favour of lithium; however, it should be noted that extent of the bias remains unknown.

The economic analysis found that augmenting with lithium was cheaper and more effective than augmenting with AAP. However, these results should be interpreted with caution in light of the sensitivity of the model to changes in the efficacy parameters and the uncertainty around the clinical data. In addition, it is expected that the price of AAPs will fall once generic versions of branded treatments are available. It is also important to note that the trials included in the MTC did not report on all of the outcomes of interest for the economic model and consequently some of the required parameters were generated using sampling methods that have not been previously validated. There was also a paucity of RCT data on follow-up and maintenance treatment.

Conclusions

The results of this review support the conclusion that augmentation of SSRIs with lithium or AAP is likely to be beneficial in people with TRD, defined as a failure to respond to two or more antidepressants in the current episode of depression. However, based on the limited number of RCTs identified, the clinical

evaluation suggests there is no statistically significant difference between the two augmentation strategies. There is a general paucity of trial data available in patients with TRD for SSRI + lithium and SSRI + AAP.

The cost-effectiveness results suggest that augmentation with lithium is cheaper and more effective compared with augmenting with AAP. However, the results are not definitive because the model is sensitive to the clinical effectiveness parameters of discontinuations and treatment response. The cost-effectiveness of SSRI + lithium and SSRI + AAP will need to be reconsidered if further trial data become available.

Suggested research priorities

A RCT in patients with TRD that compares SSRI + lithium with SSRI + AAP for response, remission and discontinuation in both the acute and maintenance phases of treatment is needed. In addition, data on relapse rates in the long term would be beneficial. Adverse events and QoL data should also be prioritised as part of the research.

Study registration

This study is registered as PROSPERO CRD42011001464.

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