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Extended Research Article

Clinical and cost-effectiveness of lithium versus quetiapine augmentation for treatment-resistant depression in adults: LQD a pragmatic randomised controlled trial

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Published May 2025
DOI: 10.3310/YQVF5347

Scientific summary

Clinical and cost-effectiveness of lithium versus quetiapine augmentation for treatment-resistant depression in adults: LQD a pragmatic randomised controlled trial

Health Technology Assessment 2025; Vol. 29: No. 12
DOI: 10.3310/YQVF5347

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Major depressive disorder (MDD) is a highly prevalent and disabling illness. Between 20% and 50% of those with MDD do not respond to first- and second-line treatments, termed treatment-resistant depression (TRD). Clinical guidelines recommend augmentation with lithium or atypical antipsychotics as one treatment option for TRD. However, few studies have compared these options directly, and none have included a long-term follow-up, which is imperative given the long-term course of TRD.

Objectives

This trial aimed to examine whether it is more clinically and cost-effective to prescribe lithium or quetiapine augmentation therapy for patients with TRD over the course of 12 months.

Methods

This was a phase 4, 12-month, parallel-group, pragmatic, open-label, superiority trial comparing the clinical and cost-effectiveness of lithium versus quetiapine augmentation treatment to antidepressant medication in patients with TRD. Two arms were randomised 1 : 1 to the decision to prescribe either lithium or quetiapine, stratified by baseline depression severity, TRD severity and recruitment site. Trial clinicians received information on titration and dosing in line with current clinical guidelines. After randomisation, pre-prescribing safety checks were undertaken as per standard care and trial clinicians decided whether to proceed with prescribing the allocated medication. Subsequent decisions as to whether to continue treatment followed standard care guidelines and clinician judgement. Participants were followed up over 12 months, regardless of medication status.

Participants were recruited from six NHS mental health trusts across England. Participants were identified through secondary care clinics or consent for contact initiatives within these trusts, community and online advertisements, and primary care services. Inclusion criteria were: (1) under the care of a general practitioner and/or adult mental health service, (2) current episode of depression meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition criteria for MDD, (3) a Hamilton Depression Rating Scale-17 item score ≥ 14 at screening, (4) aged ≥ 18 years, (5) meet criteria for TRD, defined as failing to adequately respond to at least two therapeutic antidepressant treatment trials in the current episode, (6) current antidepressant treatment at or above a therapeutic dose for ≥ 6 weeks. Exclusion criteria were: (1) a diagnosis of bipolar disorder or current psychosis; (2) adequate use of lithium or quetiapine during the current episode; (3) current use of another atypical antipsychotic, (4) known contraindication to lithium or quetiapine; (5) participation in another Clinical Trial of an Investigational Medicinal Product; (6) insufficient comprehension or attention to engage in trial procedures, (7) pregnancy, trying for pregnancy, or breastfeeding. Participants attended a screening and baseline visit, usually on the same day. Randomisation took place on the same day as the baseline visit. Participants attended visits at the hospital at weeks 8, 26 and 52, and completed weekly assessments via the True Colours app.

The primary outcome measures were depressive symptom severity over 52 weeks, measured weekly using the self-rated Quick Inventory of Depressive Symptomatology (QIDS-SR), and time to all-cause treatment discontinuation of the trial medication. Secondary outcome measures included clinician-rated depression severity (Montgomery–Åsberg Depression Rating Scale, MADRS), response and remission rates (MADRS), health-related quality of life (EuroQol-5 Dimensions, EQ-5D), work and social functioning (Work and Social Adjustment Scale, WSAS), adherence to the trial medication (5-item Medication Adherence Report Scale, MARS-5), weight, blood pressure, clinician-rated global improvement (Clinical Global Impression scale, CGI), side effects (Patient Rated Inventory of Side Effects, PRISE), time to initiation of the trial medication, time to initiation of any new intervention for depression and serious adverse events

(SAEs) between the two treatment arms. The MADRS and CGI were assessed by blind raters. Service use (for the economic analysis) was measured using the Client Service Receipt Inventory.

Primary efficacy analyses were conducted under intention-to-treat (ITT) and per-protocol (PP) assumptions, the latter including only those where the prescription was implemented by clinicians after the pre-prescription safety checks. The QIDS-SR outcome was analysed using a linear mixed model with weekly scores as the dependent variable, and treatment allocation, randomisation stratification variables, time and time by treatment interaction terms as explanatory variables, using an area under the curve (AUC) approach. The time to discontinuation of trial medication outcome was analysed using survival analysis methods. Cox regression models were used to estimate the hazard ratio for discontinuation, with treatment allocation and randomisation stratification variables as independent variables. Restricted mean survival time models were also used, since the Cox regression modelling showed evidence of non-proportional hazards. Time to initiation and time to new intervention for depression were also analysed in this way. Continuous secondary outcome measures were analysed similarly to the QIDS-SR outcome, using linear mixed models, but with data from weeks 8, 26 and 52 as dependent variables. Binary secondary outcomes were modelled using longitudinal logistic mixed models with data from weeks 8, 26 and 52 as dependent variables. Both types of outcome models had treatment allocation, time, time by treatment interaction terms and stratification variables as explanatory variables.

Sensitivity analyses were performed on the two primary outcomes; effects were re-estimated for: (1) participants who had a therapeutic treatment trial of the trial medication, (2) participants who reported themselves adherent to the trial medication, defined as 80% or greater adherence on the MARS-5 during the time they were taking the medication, (3) participants who were both prescribed and reported initiating treatment, (4) scenarios evaluating the effect of departures from the missing at random (MAR) assumption, and (5) subsets defined as being before and after the COVID-19 pandemic started.

The economic analysis compared costs between the two treatment arms over 52 weeks and was conducted under the ITT assumption. The primary analysis was conducted from an NHS and Personal Social Services (PSS) perspective (service use and drug costs), using quality-adjusted life-year (QALY) as the effectiveness outcome. Secondary analyses were conducted to explore (1) costs from a societal perspective (i.e. productivity loss in addition to NHS and PSS costs), and (2) using the QIDS-SR as the effectiveness outcome. Mean difference in cost between arms were estimated from generalised linear models with gamma family and log link with participants' baseline costs and randomisation stratification variables as covariates. Results of the cost effectiveness analysis were reported as incremental cost-effectiveness ratios and incremental net benefit. Sensitivity analyses examined cost-effectiveness when (1) the generic unit cost of the trial drugs were used instead of the cheapest (as in the primary analysis), (2) covariate dependent MAR was assumed for missing data, and (3) the analysis was modified to adjust for the impact of the COVID-19 pandemic.

The sample size was revised to 214 in April 2020 due to challenges with recruitment. With an expected 10% loss at follow-up, a log-rank test for the time to trial treatment discontinuation (50% lithium, 70% quetiapine remaining on treatment) would have 80% power. For the QIDS-SR outcome, simulation and the non-central chi-squared method provided a value of 96.5% power to detect an effect size of 0.38 (a minimum clinically significant difference between treatments), with 40% occasion-wise nonresponse assumed.

Results

Two hundred and twelve participants were randomised, 107 to quetiapine and 105 to lithium. Of those randomised to quetiapine, 95 were prescribed and initiated the medication. Of those allocated to lithium, 86 were prescribed and 84 initiated the medication. Of those who initiated the medication, 38.9% of participants randomised to quetiapine and 50.0% of those randomised to lithium discontinued before 12 months. The main reasons for discontinuation in both arms were side effects and inadequate clinical response.

For the time to discontinuation outcome, 1% of participants in the lithium arm were missing data and none in the quetiapine arm. For the QIDS-SR outcome, 19.6% of participants in the quetiapine arm and 16.2% in the lithium arm

were missing data at week 8, 25.2% in the quetiapine arm and 39.0% in the lithium arm were missing data at week 26, and 28.0% in the quetiapine arm and 35.2% in the lithium arm were missing data at week 52. In the ITT analysis, the area under the quetiapine versus lithium QIDS-SR difference curve (AUC) from the fully adjusted model was −68.36, with a confidence interval (CI) of −129.95 to −6.76, excluding the null value of no difference, indicating lower levels of depression in the quetiapine arm compared to the lithium arm over the 52-week study period (p = 0.0296). Median time to discontinuation in the quetiapine arm was 365.0 days (25th–75th percentile 57.0–365.0), and 212.0 days (21.0–365.0) in the lithium arm. Participants in the quetiapine arm had 0.72 times the hazard of discontinuing (95% CI: 0.47 to 1.09, i.e. hazard 28% less in quetiapine arm) compared to those in the lithium arm, but the null value of one/the same hazard in each group, could not be excluded. Primary outcome PP analyses gave similar results.

Regarding secondary outcomes, participants in the quetiapine arm scored 2.98 points lower (95% CI: −5.87 to −0.09, p = 0.0435) on the MADRS compared to those in the lithium arm at 52 weeks. Similarly, participants in the quetiapine arm scored 3.64 points lower (95% CI: −6.28 to −0.99) on the WSAS than those in the quetiapine arm at 52 weeks (p = 0.0071). There was no difference between arms at 8 weeks. There were no differences in weight, blood pressure, PRISE scores or MARS-5 scores between arms at either time point. At week 8, participants in the quetiapine arm had 1.95 times the odds (95% CI: 0.50 to 7.68) of responding compared to those in the lithium arm. This difference was larger at 52 weeks, with participants in the quetiapine arm having 3.67 times the odds of responding (0.94–14.25, p = 0.0607). There was little evidence of a difference between arms in remission or global improvement. Participants in the quetiapine arm had 2.22 times the odds of reaching remission at 8 weeks (0.41–11.95), and 1.38 times the odds at 52 weeks (0.29–6.60) compared to the lithium arm. Participants in the quetiapine arm had 1.23 times the odds (0.35–4.39) and 1.12 times the odds (0.32–3.92) of global improvement as compared to those in the lithium arm. Time to initiation of the trial medication and time to initiation of a new treatment for depression did not significantly differ between the two arms. There were 32 SAEs from 18 participants recorded during the trial, 15 from 7 participants randomised to quetiapine and 17 from 11 participants randomised to lithium. The majority were not related or unlikely related to the trial medication, although one event was possibly related to lithium treatment.

Sensitivity analyses suggested primary outcome effects were similar to the ITT analysis when re-estimated in (1) participants who received a therapeutic treatment trial, (2) participants who initiated the trial medication, (3) participants who were randomised or attended study visits before the COVID-19 pandemic and (4) participants who self-reported as being treatment adherent. In exploring missing data assumptions at 52 weeks only, a 0.2 points or greater worsening on the QIDS-SR in the quetiapine arm only would have been needed to render the difference between arms non-significant; however, assuming this worsening only in the quetiapine arm seems a strong assumption.

Regarding health-related quality of life, there were no differences between arms at baseline. However, at week 8 and week 26, participants in the quetiapine arm had significantly better quality of life than those in the lithium arm. This difference became non-significant at week 52. Mean QALY gain between baseline and 52-week follow-up was 0.540 for the quetiapine arm and 0.468 for the lithium arm. The adjusted difference was 0.074 in favour of quetiapine with a 99.5% chance that quetiapine led to improved QALY. There were no significant differences between arms in total NHS or total societal costs are baseline. Over the 52-week follow-up period, the quetiapine arm had a lower healthcare cost (−£472.32, 95% CI: −£1111.12 to £166.47) and a higher societal cost (162.90, 95% CI: −£1224.13 to 1549.94) compared to the lithium arm, with probabilities of the quetiapine arm being cost saving of 0.94 and 0.45, respectively.

In the NHS and PSS cost-effectiveness analysis, quetiapine was associated with a lower cost and a higher QALY gain, and therefore dominated lithium. At NICE's £20,000 willingness to pay (WTP) threshold per additional unit of QALY, the probability that quetiapine was more cost effective was 0.99. When adopting a societal perspective, quetiapine was associated with a higher cost and a higher QALY, with a probability of quetiapine being more cost effective of 0.91. Analyses also indicated that quetiapine was more cost-effective when using the QIDS-SR as the effectiveness outcome. Quetiapine appeared to be less cost-effective in sensitivity analyses compared to the base case scenario; however, in all sensitivity analyses, quetiapine remained the more cost-effective option, according to the NICE £20,000 WTP threshold for one additional unit of QALY.

Conclusions

Clinical guidelines for the treatment of depression currently recommend lithium or second-generation antipsychotics as first-line augmentation options for those who have not responded to antidepressants alone. However, evidence for these options mainly derives from studies in which lithium was added to tricyclic antidepressants (TCAs) and antipsychotics to selective serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors. Further, very few studies have directly compared these options head-to-head or over the longer term. This trial aimed to provide evidence for clinicians and patients when choosing between augmentation options for TRD. Overall, our results suggested that quetiapine was superior to lithium augmentation therapy in reducing symptoms of depression and cost-effectiveness. Patients randomised to quetiapine showed a greater reduction in QIDS-SR scores over 12 months compared to those randomised to lithium. This effect was also reflected in some of the secondary outcome measures: compared to the lithium arm, those randomised to quetiapine showed significantly lower MADRS and WSAS scores at week 52, but not week 8, and significantly better EQ-5D scores at week 8, but not week 52. Although those who were randomised to quetiapine showed a longer time to discontinuation than those randomised to lithium, this difference was not statistically significant. Similarly, the direction of effects for several of the other secondary outcomes also favoured quetiapine (i.e. MADRS response and remission, CGI-I), but were not statistically significant.

A limitation of the study was the substantial proportions of missing data for some of the secondary outcome measures, limiting our confidence in these results. A significant strength was the long-term follow-up period of 52 weeks with longitudinal weekly symptom measures, since patients with TRD often show a fluctuating response not captured by less frequent cross-sectional measures. Our results extend previous findings from trials with short-term follow-up periods, suggesting moderate clinically relevant benefit of quetiapine over lithium on depression levels in the longer-term, although there was not strong evidence for a difference in discontinuation. Relatedly, the open-label, pragmatic design of the trial, whereby prescribing was continued by participants' primary or secondary care teams, gives insight into the effectiveness of recommended augmentation therapies for TRD in clinical practice. Additionally, future research should explore predictors of treatment response to establish whether there are additional factors which may inform treatment choice.

Trial registration

This trial is registered as ISRCTN16387615.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 14/222/02) and is published in full in *Health Technology Assessment*; Vol. 29, No. 12. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.5

A list of Journals Library editors can be found on the NIHR Journals Library website

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This article

The research reported in this issue of the journal was funded by the HTA programme as award number HTA 14/222/02. The contractual start date was in May 2016. The draft manuscript began editorial review in June 2023 and was accepted for publication in July 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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