



Clinical and cost-effectiveness of lithium versus quetiapine augmentation for treatment-resistant depression: a pragmatic, open-label, parallel-group, randomised controlled superiority trial in the UK

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Summary

Background Lithium and quetiapine are first-line augmentation options for treatment-resistant depression; however, few studies have compared them directly, and none for longer than 8 weeks. We aimed to assess whether quetiapine augmentation therapy is more clinically effective and cost-effective than lithium for patients with treatment-resistant depression over 12 months.

Methods We did this pragmatic, open-label, parallel-group, randomised controlled superiority trial at six National Health Service trusts in England. Eligible participants were adults (aged ≥ 18 years) with a current episode of major depressive disorder meeting DSM-5 criteria, with a score of 14 or higher on the 17-item Hamilton Depression Rating Scale at screening who had responded inadequately to two or more therapeutic antidepressant trials. Exclusion criteria included having a diagnosis of bipolar disorder or current psychosis. Participants were randomly assigned (1:1) to the decision to prescribe lithium or quetiapine, stratified by site, depression severity, and treatment resistance, using block randomisation with randomly varying block sizes. After randomisation, pre-prescribing safety checks were undertaken as per standard care before proceeding to trial medication initiation. The coprimaries outcomes were depressive symptom severity over 12 months, measured weekly using the Quick Inventory of Depressive Symptomatology, and time to all-cause treatment discontinuation. Economic analyses compared the cost-effectiveness of the two treatments from both an NHS and personal social services perspective, and a societal perspective. Primary analyses were done in the intention-to-treat population, which included all randomly assigned participants. People with lived experience were involved in the trial. The trial is completed and registered with the International Standard Randomised Controlled Trial registry, ISRCTN16387615.

Findings Between Dec 5, 2016, and July 26, 2021, 212 participants (97 [46%] male gender and 115 [54%] female gender) were randomly assigned to the decision to prescribe quetiapine ($n=107$) or lithium ($n=105$). The mean age of participants was 42.4 years (SD 14.0 years) and 188 (89%) of 212 participants were White, seven (3%) were of mixed ethnicity, nine (4%) participants were Asian, four (2%) were Black, three (1%) were of Other ethnicity, and ethnicity was not recorded for one (1%) participant. Participants in the quetiapine group had a significantly lower overall burden of depressive symptom severity than participants in the lithium group (area under the between-group differences curve -68.36 [95% CI -129.95 to -6.76 ; $p=0.0296$). Time to discontinuation did not significantly differ between the two groups. Quetiapine was more cost-effective than lithium. 32 serious adverse events were recorded in 18 participants, one of which was deemed possibly related to the trial medication in a female participant in the lithium group. The most common serious adverse event was overdose, occurring in three (3%) of 107 participants in the quetiapine group (seven events) and three (3%) of 105 participants in the lithium group (five events).

Interpretation Results of the trial suggest that quetiapine is more clinically effective than lithium as a first-line augmentation option for reducing symptoms of depression in the long-term management of treatment-resistant depression, and is probably more cost-effective than lithium.

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Introduction

Major depressive disorder is a leading cause of disability globally and results in substantial societal and health-care costs.¹ Antidepressants and psychological therapy are

recommended treatments² but are ineffective for 20–50% of people with depression, who are typically then considered to have treatment-resistant depression.³ Treatment-resistant depression has a poorer prognosis,

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Research in context

Evidence before this study

For people with depression who have not responded to initial treatment with antidepressants or psychological therapy, one of the recommendations from guidelines is to augment antidepressant treatment with lithium or atypical antipsychotics, including quetiapine, aripiprazole, olanzapine, or risperidone. This trial was done in response to a 2013 National Institute for Health and Care Research Health Technology Assessment evidence synthesis, which aimed to estimate the clinical and cost-effectiveness of lithium or atypical antipsychotics for treatment-resistant depression. The evidence synthesis involved a search of Cochrane Central Register for Controlled Trials, Embase, MEDLINE, PsycINFO, and the National Health Service (NHS) Economic Evaluation Database for randomised controlled trials comparing augmentation of SSRI antidepressant therapy with either lithium or atypical antipsychotics. The search terms included terms related to depression, antidepressants, treatment resistance, randomised controlled trials, augmentation, lithium, and atypical antipsychotics. No language restrictions were applied. A mixed-treatment comparison (including six randomised controlled trials of SSRI plus atypical antipsychotic augmentation and one trial of SSRI plus lithium augmentation) did not identify any significant differences in clinical effectiveness on most outcomes. Four economic evaluations of the management of treatment-resistant depression and five studies reporting health-state utility values were also included. The annual cost per patient treated with an SSRI and lithium was estimated to be £4739 compared with £5644 for those treated with SSRI and atypical antipsychotic, with a difference of around £905 per person per year, in favour of augmentation with lithium. Since the publication of the evidence synthesis, two randomised controlled trials have compared effectiveness of lithium versus antipsychotic augmentation. One small trial (n=30) compared olanzapine, aripiprazole, and lithium augmentation of paroxetine in paroxetine-resistant patients, finding similar response rates between groups at week 4. One large trial compared quetiapine with lithium augmentation of antidepressant treatment,

finding that extended-release quetiapine augmentation (n=231) and extended-release quetiapine monotherapy (n=228) were non-inferior to lithium augmentation (n=229) at week 6. No trials compared augmentation options for longer than 8 weeks. Since treatment-resistant depression is a long-term condition with high rates of relapse and chronicity, there is little evidence available to clinicians and patients when choosing between augmentation options for long-term management of treatment-resistant depression.

Added value of this study

This trial was pragmatic and designed to reflect real-world clinical practice, within the constraints of a clinical trial. Participants were randomly assigned to the decision to prescribe lithium or quetiapine augmentation therapy, as would occur in the clinic, and then initiation of the treatment after safety checks and continuation thereafter proceeded as per standard care. Our results suggested that augmentation with quetiapine was more effective than lithium in reducing symptoms of depression in patients with treatment-resistant depression, with a benefit sustained over 12 months. There was no strong evidence for a difference in time to discontinuation of the trial medication. Quetiapine was more cost-effective from an NHS and personal social services perspective (including health-care and social care system costs) and from a societal perspective (considering productivity loss in addition to NHS and personal social services costs).

Implications of all the available evidence

Compared with lithium, quetiapine might be a more appropriate first-line augmentation for many people with treatment-resistant depression. Future research should investigate predictors of treatment response and discontinuation (eg, type of antidepressant, psychiatric comorbidity, and depression chronicity and subtype), to establish whether there are additional factors that might guide choice of augmentation treatment.

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See Online for appendix

higher mortality, worse physical health outcomes, and higher health-care and indirect economic costs than non-treatment resistant depression.⁴⁻⁸

Pharmacological treatment options for treatment-resistant depression include increasing antidepressant dosage, switching antidepressant, or adding a second medication, which we will refer to as augmentation hereafter.⁹ Although frequently used, evidence supporting dose increase is poor, especially for SSRIs.¹⁰ Switching antidepressant is recommended for non-response or poor tolerability, but it has variable response rates¹¹ that decrease with subsequent switches.³ Augmentation is recommended for patients in whom switching antidepressants has not been effective, or following

partial response and good tolerability of the current antidepressant.⁹

Augmentation with both lithium and atypical antipsychotics (including quetiapine) is effective for treatment-resistant depression,¹² and is recommended by clinical guidelines.⁹ However, few studies have compared the treatments head-to-head, providing little evidence for clinicians and patients when choosing between them. Two studies compared lithium and quetiapine augmentation in people with major depressive disorder with poor response to at least one antidepressant.^{13,14} A small, 8-week, open-label trial reported greater improvement from day 14 onwards with quetiapine than lithium.¹³ A larger study found quetiapine was non-inferior to

lithium over 6 weeks, with less severe depressive symptoms observed with quetiapine at days 4, 8, and 22, but this difference was not statistically significant.¹⁴ Notably, neither trial undertook longer-term follow-up, which is imperative as treatment-resistant depression is frequently chronic and of fluctuating severity.¹⁵

Both quetiapine and lithium are first-choice augmentation options in most clinical guidelines.¹⁶ Quetiapine is also the only atypical antipsychotic with a UK licence in treatment-resistant depression, and its short-term efficacy versus lithium is established.^{13,14} We aimed to examine whether it is more clinically effective and cost-effective over 12 months to prescribe quetiapine versus lithium augmentation therapy for patients with treatment-resistant depression. We hypothesised there would be greater reductions in depressive symptoms and a longer time to trial medication discontinuation in the quetiapine group than the lithium group over 12 months.

Methods

Study design and participants

The Lithium versus Quetiapine in treatment resistant Depression (LQD) trial was a phase 4, pragmatic, open-label, parallel-group, randomised controlled superiority trial, comparing the clinical effectiveness and cost-effectiveness of lithium versus quetiapine augmentation of antidepressant medication in participants with treatment-resistant depression. Given that recommendations for antidepressant treatment are for at least 9–12 months of continuation treatment,⁹ we chose a 12-month trial duration, with weekly assessments. The study was designed to reflect clinical practice within the constraints of a clinical trial, and participants were therefore randomly assigned to the decision to prescribe either lithium or quetiapine; trial clinicians could then decide whether to proceed with prescription of the allocated trial medication based on pre-prescribing safety checks and clinical judgement. Decisions about continuing treatment followed standard care thereafter, with handover to primary or secondary care as appropriate. All participants, regardless of trial medication status, were followed up over 12 months unless they actively withdrew.

Participants were recruited from six sites in England (South London and Maudsley National Health Service [NHS] Foundation Trust; Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust; Oxford Health NHS Foundation Trust; Tees, Esk and Wear Valleys NHS Foundation Trust; Sussex Partnership NHS Foundation Trust; and Avon and Wiltshire Mental Health Partnership NHS Trust) through secondary or tertiary care clinics, consent for contact initiatives, community or online advertisements, and participant identification centres (including primary care).

Eligible participants were adults (aged ≥ 18 years) under the care of a general practitioner (GP) or adult mental health service who had a current episode of depression meeting DSM-5 criteria for major depressive

disorder (single or recurrent episode) using the Mini International Neuropsychiatric Interview (MINI; 7·0);¹⁷ a score of 14 or higher on the 17-item Hamilton Depression Rating Scale (HAMD-17)¹⁸ at screening; inadequate response of the current episode to two or more antidepressants, prescribed for at least 6 weeks at therapeutic dose, according to Maudsley Prescribing Guidelines¹⁹ or the British National Formulary; current antidepressant treatment unchanged and at therapeutic dose for at least 6 weeks; and provided written informed consent. The cutoff of 14 on the HAMD-17 was chosen to reflect a pragmatic minimum severity of depression in the context of treatment-resistant depression, which often presents with chronic but fluctuating levels of severity or a partial response to an antidepressant, or both. Individuals were excluded if they had a diagnosis of bipolar disorder or current psychosis on the MINI 7·0; adequate use of lithium or quetiapine during their current episode; current use of another atypical antipsychotic; known contraindication to lithium or quetiapine; current participation in another clinical trial; an insufficient degree of comprehension or attention to engage in trial procedures; or were pregnant or actively trying for pregnancy, or breastfeeding.

People with lived experience were involved in designing (providing feedback on the protocol and patient-facing documents) and running the trial (providing feedback on recruitment methods and participating as members of the trial steering committee). The trial received a favourable opinion from the East of England–Cambridge South Research Ethics Committee and was approved by the Health Research Authority and the Medicines and Healthcare products Regulatory Agency (EudraCT 2016–001637–27). The protocol has been published previously.²⁰ The trial was registered with the International Standard Randomised Controlled Trial registry, ISRCTN16387615.

Randomisation and masking

Participants were randomly assigned (1:1) to the decision to prescribe lithium or quetiapine, stratified by site (London, Oxfordshire, North East England, Bristol, and Brighton), depression severity (HAMD-17 baseline score of moderate 14–18, severe 19–22, or very severe ≥ 23), and degree of treatment resistance (failure of two versus three or more antidepressant treatments in the current episode), using block randomisation with randomly varying block sizes. Randomisation was conducted using a web-based service hosted by King's Clinical Trials Unit (King's College London, London, UK) after completion of baseline measures. Researchers, clinicians, and participants were aware of treatment allocation; however, clinician-rated outcome measures (Montgomery–Åsberg Depression Rating Scale [MADRS]²¹ and the Clinical Global Impression [CGI] scale²²) were assessed by masked raters, and statisticians were unaware of group allocation until the

data analysis phase (see statistical analysis plan, appendix pp 2–35).

Procedures

Treatment decisions were at the clinical discretion of trial clinicians. They received recommendations for titration and dosing in accordance with current best practice guidelines (appendix p 37), aiming for a lithium plasma concentration of 0.6–1.2 mmol/L, or 150–300 mg quetiapine per day, and they were advised to keep participants' existing antidepressant treatment at a stable, therapeutic dose.

A flow chart of trial procedures is in the protocol.²⁰ Research visits took place at screening and weeks 8, 26, and 52 after randomisation. Weekly self-rated Quick Inventory of Depressive Symptomatology (QIDS-SR),²³ Work and Social Adjustment Scale (WSAS),²⁴ and trial medication status were administered via an online platform, True Colours. If a patient reported not taking trial medication for two consecutive weeks, they were contacted to confirm discontinuation, date, and reason for discontinuation. These self-reported data were supplemented with information from medical records and prescribing clinicians.

Outcomes

The coprimary outcomes were overall burden of depressive symptom severity over 12 months (measured by area under the between-group differences curve in self-rated weekly QIDS-SR) and time to all-cause treatment discontinuation (defined as the time at which participants stopped taking the trial medication). Secondary outcomes were clinician-rated depression severity (measured by MADRS total score); the proportion of participants with a response ($\geq 50\%$ reduction in MADRS total score); the proportion of participants in remission (MADRS total score ≤ 10); health-related quality of life (measured by EQ-5D²⁵ summary index score, reported as part of health economic analyses); work and social functioning (measured by WSAS total score); treatment adherence (measured by 5-item Medication Adherence Report Scale score [MARS-5]²⁶); bodyweight; blood pressure; global improvement (proportion of participants with a CGI-Improvement score of much or very much improved); side-effects (measured by Patient Rated Inventory of Side Effects [PRISE]²⁷ total score); time to initiation and proportion of participants initiating trial medication; time to initiation and proportion of participants initiating any new intervention for depression; serious adverse events, serious adverse reactions; and suspected unexpected serious adverse reactions (SUSARs). Common adverse events were not recorded as the profiles of both treatments are well known. All secondary outcomes were measured at 8 and 52 weeks, with the same measures assessed at 26 weeks as tertiary outcomes. Planned tertiary outcomes and ancillary analyses are presented in

the protocol;²⁰ of these, only the economic analysis will be reported in this paper, which used the Client Service Receipt Inventory,²⁸ modified for treatment-resistant depression, collected at baseline, and 8, 26, and 52 weeks. The Client Service Receipt Inventory contains data on health-care service use, including the number and duration of contacts with primary health-care services such as GP visits, practice nurse consultations, and community psychiatric services. All other tertiary and ancillary analyses²⁰ will be published elsewhere.

Choice of primary outcome measure

The QIDS-SR has strong psychometric properties, is sensitive to symptom change,²³ and is short enough to be administered weekly without being too burdensome. We chose to use all weekly QIDS-SR data (rather than a single timepoint outcome), since participants with treatment-resistant depression often have symptoms that fluctuate in severity.²⁹ Patient and public involvement members were supportive of weekly QIDS-SR assessments as a better indication of long-term outcome, and they felt that participants might benefit from frequent assessments. Given the nature of treatment-resistant depression, it was expected that a substantial proportion of participants would not experience sufficient sustained benefit from the trial medication, and that they would discontinue before 12 months. To capture this aspect of efficacy, time to all-cause discontinuation was chosen as the coprimary outcome.

Statistical analysis

Statistical input followed King's Clinical Trials Unit standard operating procedures. The statistical analysis plan and a short list of deviations are provided in the appendix (pp 2–36). During the trial, the sample size was reduced from 276 to 214 due to challenges with recruitment. With a sample size of 214, and assuming 10% attrition, 192 participants would be expected to have complete data. Using the log-rank test and assuming a discontinuation rate of 50% for lithium and 30% for quetiapine (hazard ratio 1.94) would provide 80% power for the time to discontinuation outcome.²⁰ For the weekly QIDS-SR outcome, this sample size would provide 96.5% power for an effect size of 0.38, assuming a non-response rate of 40% at the main research visits. An α of 0.05 was assumed for each outcome.

Variables were summarised using means and standard deviations, medians and IQRs, frequencies and proportions, or Kaplan-Meier methods.

Clinical effectiveness analyses were done in the intention-to-treat (ITT) population, which included all randomly assigned participants, and the per-protocol population, which included only participants who were prescribed the randomised trial medication. The QIDS-SR outcome was analysed using a linear mixed model with random intercepts and slopes; weekly scores as the

dependent variable; and treatment allocation, randomisation stratification variables, baseline QIDS-SR, baseline variables that predicted missing QIDS-SR data at 52 weeks (White or Other ethnicity and number of MINI psychiatric comorbidities), continuous time, and time by treatment interaction terms as explanatory variables. The area under the curve (used to reflect difference over the whole follow-up period and the fluctuating nature of depression) of the quetiapine versus lithium estimated differences for each week was calculated using the trapezoid rule.³⁰ The time to trial medication discontinuation outcome was analysed using survival analysis methods. The discontinuation date was either: the recorded discontinuation date, the withdrawal date, the last known follow-up date, or the 52 week follow-up point date, whichever occurred first. Individuals who were not prescribed or did not initiate the trial medication were assigned a discontinuation time of 0.5 days. Cox regression models were used to estimate the hazard ratio for discontinuation, with treatment allocation and randomisation stratification variables as independent variables. Time to initiation of the trial medication and time to new intervention for depression were analysed using the same method.

Continuous secondary outcome measures were analysed using linear mixed models with random intercepts only, week 8, 26, and 52 outcomes as dependent variables (26-week measures were included to maximise use of data and benefits of mixed models, but since outcomes at this timepoint were tertiary, between-group differences at 26 weeks were not reported in this paper), and treatment allocation, stratification variables, baseline measure of the relevant variable, categorical time, and time by treatment interaction terms as explanatory variables. Binary secondary outcomes were modelled similarly using longitudinal logistic mixed models. Significant secondary outcome *p* values were also compared to a Hochberg's improved Bonferroni critical value.³¹ False discovery rates (not prespecified in the statistical analysis plan) of 5%, 10%, and 20% were used. Serious adverse events, serious adverse reactions, and SUSARs were summarised as the type and number of events and number of participants who experienced events. Safety endpoints were assessed in the intention-to-treat population. Sensitivity analyses were performed for both primary outcomes; effects were re-estimated for: (1) participants who initiated the trial medication; (2) participants who had a therapeutic treatment trial of the trial medication; (3) participants adherent to the trial medication (defined as $\geq 80\%$ adherence on the MARS-5); (4) scenarios evaluating the effect of departures from the missing at random assumption; and (5) excluding participants randomly assigned after the COVID-19 pandemic started or with outcome measures taken after COVID-19 measures were implemented.

The economic analysis (appendix pp 38–43) compared the cost-effectiveness of the two treatments over 52 weeks and was conducted under the ITT assumption. The

primary analysis was conducted from an NHS and personal social services perspective (including costs to the health-care and social care systems), using quality-adjusted life-years (QALYs) as the effectiveness outcome. Secondary analyses were conducted to explore the cost-effectiveness from a societal perspective (ie, productivity loss in addition to NHS and personal social services costs) and using the QIDS-SR as the effectiveness outcome. Mean differences in cost-effectiveness between groups were estimated using bootstrapped generalised linear models with γ family and log link with participants' baseline costs and randomisation stratification variables as covariates, with missing observations replaced with a set of imputed values through multiple imputations drawn from posterior predictive distribution given the missing observed data. The mean difference in QALYs between the two groups was estimated using bootstrapped ordinary least squares regression. The cost effectiveness analyses were reported in terms of incremental cost-effectiveness ratios and incremental net health benefit. Incremental cost-effectiveness ratios measure the additional cost per additional unit of health benefit gained by one intervention compared with another, while incremental net health benefit quantifies the difference in net health benefit between interventions, taking into account both costs and health outcomes. Sensitivity analyses examined cost-effectiveness when the generic unit cost of the trial drugs was used instead of the cheapest (as in the primary analysis), the covariate dependent missing at random was assumed for missing data, and the analysis was modified to adjust for the impact of the COVID-19 pandemic.

A data monitoring and ethics committee provided input on the development of the statistical analysis plan and health economics analysis plan and monitored progress throughout the trial, and a trial steering committee oversaw the trial. Analyses were conducted using Stata (version 17.0 or higher).

Role of the funding source

The funder commissioned research comparing lithium to other augmentation in treatment-resistant depression, but otherwise had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 5, 2016, and July 26, 2021, 212 participants (97 [46%] male gender and 115 [54%] female gender) were randomly assigned to the decision to prescribe quetiapine (*n*=107) or lithium (*n*=105; figure 1). The mean age of participants was 42.4 years (SD 14.0 years) and 188 (89%) of 212 participants were White, seven (3%) were of mixed ethnicity, nine (4%) participants were Asian, four (2%) were Black, three (1%) were of Other ethnicity, and ethnicity was not recorded for one (1%) participant (table 1). Of the 107 participants randomly assigned to quetiapine, 95 (89%) were prescribed the medication and 95 initiated the

medication. Of the 95 participants who initiated treatment, 37 (39%) discontinued treatment before 12 months. Of the 105 participants randomly assigned to lithium, 86 (82%) were prescribed the medication and 84 (80%) initiated the medication. Of those who initiated, 42 (50%) of 84 participants discontinued

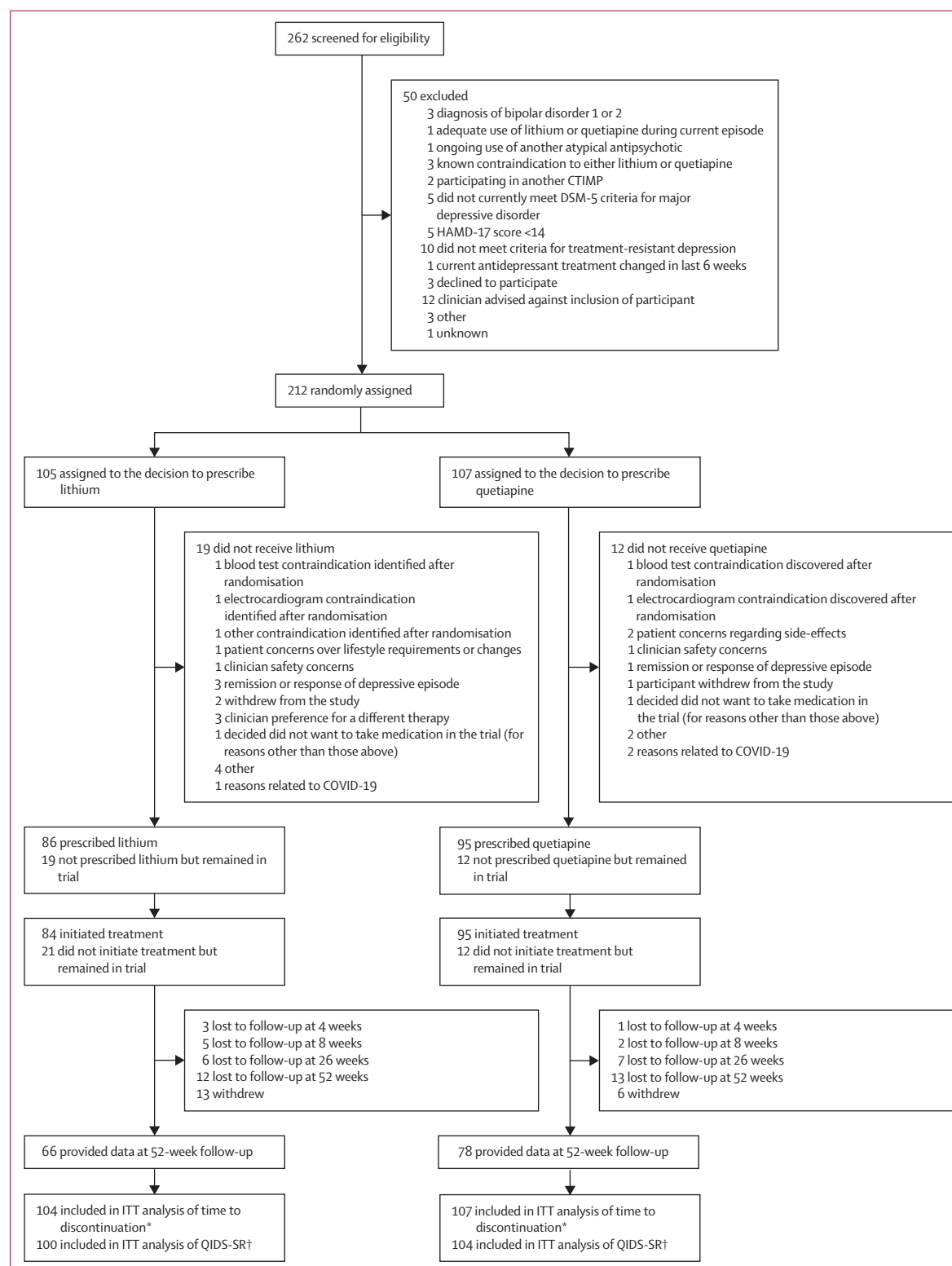


Figure 1: Trial profile
CTIMP=Clinical Trial of an Investigational Medicinal Product. HAMD-17=17-item Hamilton Depression Rating Scale. ITT=intention-to-treat. QIDS-SR=Quick Inventory of Depressive Symptomatology. *Data on discontinuation status were available for 104 of 105 participants in the lithium group and all 107 participants in the quetiapine group, and thus these participants were included in the ITT analysis of the discontinuation coprimary outcome. †100 of 105 participants in the lithium group and 104 of 107 participants in the quetiapine group provided any QIDS-SR data after randomisation, and thus were included in the ITT analysis of the depressive symptom coprimary outcome.

	Quetiapine (n=107)	Lithium (n=105)
Study site*		
Bristol	4 (4%)	5 (5%)
Brighton	7 (7%)	7 (7%)
London	42 (39%)	41 (39%)
Newcastle	26 (24%)	27 (26%)
Oxford	28 (26%)	25 (24%)
Treatment-resistant depression severity*		
Two previous antidepressants	43 (40%)	42 (40%)
More than two previous antidepressants	64 (60%)	63 (60%)
Depression severity*†		
Moderate	36 (34%)	33 (31%)
Severe	32 (30%)	33 (31%)
Very severe	39 (36%)	39 (37%)
Age, years		
Mean (SD)	41.6 (14.6)	43.2 (13.3)
Median (IQR)	40.0 (29.0–52.0)	43.0 (33.0–53.0)
Missing	0	0
Gender		
Male	42 (39%)	54 (51%)
Female	65 (61%)	50 (48%)
Intersex	0	0
Affirmed male gender	0	1 (1%)
Affirmed female gender	0	0
Neither	0	0
Missing	0	0
Ethnicity		
White	96 (90%)	92 (88%)
Mixed or multiple	4 (4%)	3 (3%)
Asian	2 (2%)	7 (7%)
Black, African, or Caribbean	2 (2%)	2 (2%)
Other	2 (2%)	1 (1%)
Unrecorded	1 (1%)	0
Missing	0	0
Highest completed level of education		
Primary education or less (no formal qualifications)	1 (1%)	6 (6%)
Secondary education (GCSE or O Levels)	16 (15%)	15 (14%)
College level education or equivalent (A Level, NVQ, International Baccalaureate, or BTEC nationals)	44 (41%)	37 (35%)
Degree level education or diploma	28 (26%)	31 (30%)
Post-graduate degree	18 (17%)	16 (15%)
Missing	0	0

(Table 1 continues in next column)

treatment before 12 months, with discontinuation date missing for one participant. Reasons for non-prescription and discontinuation are presented in the appendix (p 49). The mean dose of quetiapine was 194.7 mg (SD 135.2) and the mean dose of lithium was

	Quetiapine (n=107)	Lithium (n=105)
(Continued from previous column)		
Current main employment status		
Paid employment	54 (51%)	49 (47%)
Unemployed	29 (27%)	43 (41%)
Student	10 (9%)	4 (4%)
Housewife or househusband	1 (1%)	2 (2%)
Retired	13 (12%)	7 (7%)
Missing	0	0
Antidepressants at baseline‡		
SSRI	51 (48%)	48 (46%)
Tricyclic antidepressant	12 (11%)	9 (9%)
Monoamine oxidase inhibitor	0 (0%)	0 (0%)
Tetracyclic antidepressant (and related)	29 (27%)	33 (31%)
Serotonin–noradrenaline reuptake inhibitor	35 (33%)	39 (37%)
Serotonin modulator and stimulator	4 (4%)	4 (4%)
Noradrenaline reuptake inhibitor	0	0
Noradrenaline and dopamine reuptake inhibitor	0	0
Melatonin agonist	1 (1%)	1 (1%)
Other	1 (1%)	1 (1%)
Missing	1 (1%)	0
Received psychological therapy for depression in current episode		
Yes	71 (66%)	71 (68%)
No	34 (32%)	34 (32%)
Missing	2 (2%)	0 (0%)
Number of comorbid psychiatric diagnoses		
Mean (SD)	1.8 (1.6)	1.9 (1.5)
Median (IQR)	1.0 (0.0–3.0)	2.0 (1.0–3.0)
Missing	0	0
HAMD-17 score		
Mean (SD)	21.2 (5.0)	21.9 (5.4)
Median (IQR)	20.0 (17.0–24.0)	21.0 (18.0–25.0)
Missing	0	0
Weight, kg		
Mean (SD)	88.4 (22.5)	88.3 (22.1)
Median (IQR)	86.8 (73.4–98.6)	88.6 (71.0–102.5)
Missing	14 (13%)	6 (6%)
Waist circumference, cm		
Mean (SD)	99.3 (17.1)	101.4 (22.0)
Median (IQR)	99.0 (86.0–110.5)	99.0 (88.0–113.3)
Missing	28 (26%)	26 (25%)
Systolic blood pressure, mm Hg		
Mean (SD)	131.1 (16.8)	130.7 (17.2)
Median (IQR)	130.0 (118.5–141.0)	129.0 (120.0–143.0)
Missing	15 (14%)	14 (13%)

(Table 1 continues in next column)

	Quetiapine (n=107)	Lithium (n=105)
(Continued from previous column)		
Diastolic blood pressure, mm Hg		
Mean (SD)	77.8 (10.9)	79.7 (11.4)
Median (IQR)	79.0 (70.0–84.0)	80.0 (72.0–86.0)
Missing	16 (15%)	14 (13%)
Pulse, beats per min		
Mean (SD)	76.5 (15.2)	74.3 (12.1)
Median (IQR)	73.5 (65.0–85.0)	74.0 (66.0–82.0)
Missing	17 (16%)	16 (15%)
MARS-5 score		
Mean (SD)	23.5 (1.9)	23.2 (2.1)
Median (IQR)	24.0 (23.0–25.0)	24.0 (22.0–25.0)
Missing	3 (3%)	5 (5%)
QIDS-SR score		
Mean (SD)	17.2 (4.4)	18.0 (4.1)
Median (IQR)	17.0 (15.0–21.0)	18.0 (15.0–21.0)
Missing	0	1 (1%)
WSAS score		
Mean (SD)	27.2 (7.1)	27.9 (7.8)
Median (IQR)	28.0 (23.0–31.0)	28.4 (22.5–34.0)
Missing	1 (1%)	3 (3%)
HCL-16 score		
Mean (SD)	6.6 (3.7)	7.0 (3.9)
Median (IQR)	7.0 (4.0–10.0)	7.5 (4.0–10.0)
Missing	4 (4%)	7 (7%)
MÅDRS score		
Mean (SD)	30.8 (6.4)	31.5 (7.2)
Median (IQR)	31.0 (27.0–35.0)	30.5 (26.0–36.0)
Missing	0	1 (1%)
GAD-7 score		
Mean (SD)	12.4 (5.6)	12.6 (5.7)
Median (IQR)	13.0 (8.0–17.0)	13.0 (8.0–18.0)
Missing	0	2 (2%)
CGI-S		
Normal, not at all ill	1 (1%)	0
Borderline mentally ill	0	0
Mildly ill	10 (9%)	9 (9%)
Moderately ill	55 (51%)	55 (52%)
Markedly ill	31 (29%)	31 (30%)
Severely ill	10 (9%)	10 (10%)
Missing	0	0

Data are n (%), unless otherwise specified. The sum of some percentages do not sum to 100, due to rounding. GCE=General Certificate of Secondary Education. O Level=Ordinary Level. A Level=Advanced Level. NVQ=National Vocational Qualification. BTEC=Business and Technology Education Council. HAMD-17=17-item Hamilton Depression Rating Scale. MARS-5=5-item Medication Adherence Report Scale. QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Rated. WSAS=Work and Social Adjustment scale. HCL-16=16 item Hypomanic Checklist. MÅDRS=Montgomery-Åsberg Depression Rating Scale. GAD-7=Generalised Anxiety Disorder Questionnaire. CGI-S=Clinical Global Impression rating scale-severity. *Randomisation stratification variables. †Depression severity was defined according to baseline HAMD-17 score: moderate (score of 14–18), severe (score of 19–22), or very severe (score of ≥23). ‡Some participants were on more than one antidepressant, so percentages do not sum to 100.

Table 1: Baseline characteristics of study participants

681.3 mg (250.7). The mean peak serum lithium concentration in participants who received a documented therapeutic treatment trial (a serum level of 0.6–1.2 mmol/L and >4 weeks of treatment) was 0.85 mmol/L (SD 0.55).

Missing data at each timepoint are in the appendix (p 51).

All analyses presented followed ITT principles and per-protocol analyses are in the appendix (pp 56–57). 100 of 105 participants in the lithium group and 104 of 107 participants in the quetiapine group provided any QIDS-SR data after randomisation, and thus were included in the ITT analysis of the depressive symptoms coprimary outcome. Data on discontinuation status were available for 104 of 105 participants in the lithium group and all 107 participants in the quetiapine group, and thus these participants were included in the ITT analysis of the discontinuation coprimary outcome. For the depressive symptom coprimary outcome, over the 52-week follow-up period, participants in the quetiapine group had a lower overall burden of depressive symptom severity than participants in the lithium group (area under the difference curve –68.36 [95% CI –129.95 to –6.76]; $p=0.0296$). Mean observed and predicted weekly QIDS-SR scores showed a greater improvement in the quetiapine group over time than the lithium group (figure 2). QIDS-SR mixed model results and the trapezoid rule code are in the appendix (pp 53–54).

For the discontinuation coprimary outcome, time to trial medication discontinuation did not differ significantly between the two groups; the median time was 365.0 days (IQR 57.0–365.0) in the quetiapine group and 212.0 days (21.0–365.0) in the lithium group (adjusted hazard ratio [HR] 0.72 [95% CI 0.47–1.09]; $p=0.1196$; figure 3). The Kaplan–Meier (figure 3) and Schoenfeld residual plots (appendix p 55) indicated the proportional-hazards assumption was violated. Therefore, an estimate of the difference in days to discontinuation from a restricted mean survival time model is presented in the appendix (p 55).³² No differences were identified in the hazard of discontinuation or number of days on average remaining on trial medication between the groups in the Cox and restricted mean survival time analyses.

Estimates from the per-protocol (appendix pp 56–57) and sensitivity analyses (appendix pp 58–63) did not differ appreciably from those reported in the ITT population: depression severity was found to be lower in the quetiapine group than the lithium group and no differences were identified in time to discontinuation between groups.

In terms of secondary outcomes, participants in the quetiapine group had significantly lower MÅDRS ($p=0.0435$) and WSAS scores ($p=0.0071$) at week 52 than participants in the lithium group (appendix pp 64–65). No significant differences in adherence, as measured by

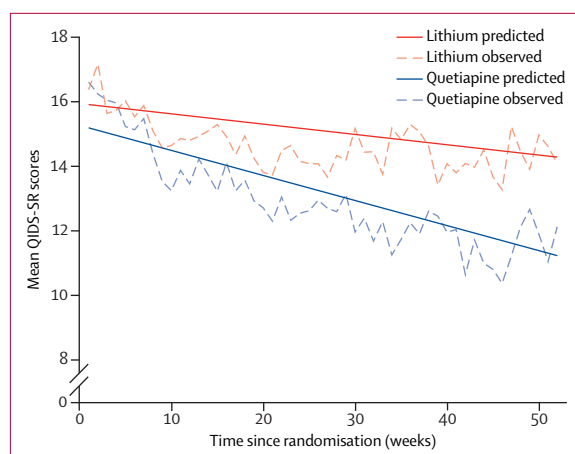


Figure 2: Observed and predicted weekly QIDS-SR scores in the intention-to-treat population
QIDS-SR=Quick Inventory of Depressive Symptomatology.

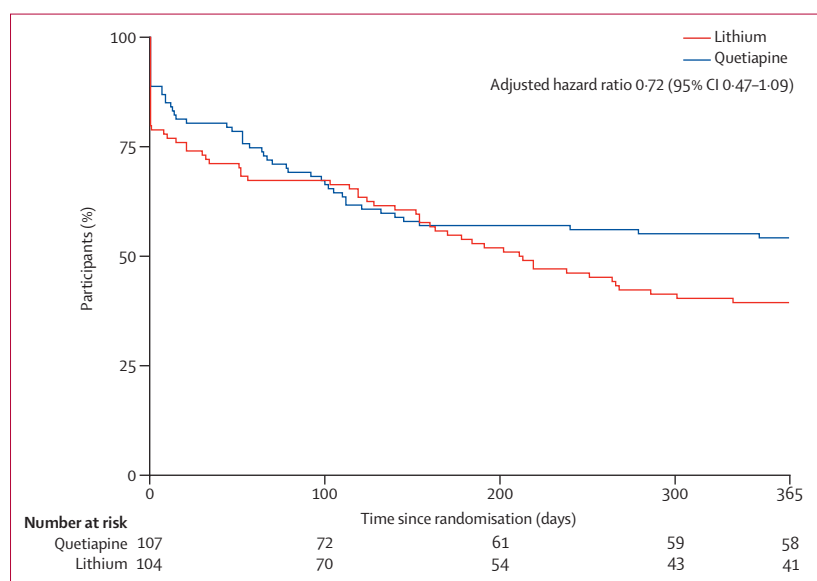


Figure 3: Kaplan-Meier estimates of time to trial medication discontinuation

the MARS-5, side-effects, as measured by the PRISE, or physical parameters (bodyweight and blood pressure) were identified between groups (appendix pp 64–65). No significant differences were identified between groups in the proportion of responders, proportion of participants in remission, or the proportion of participants classed as much or very much improved, although at week 52, 25 (23%) of 107 participants in the quetiapine group were responders versus 12 (11%) of 105 participants in the lithium group (odds ratio $p=0.0607$; appendix p 66). No significant differences in time to initiation of the trial medication and any new intervention for depression were identified between groups (appendix pp 66–69). When adjusting for multiple testing of the secondary outcomes, the between-group difference in WSAS comparison at 52 weeks remained significant at the 20%

false discovery rate. There were minimal differences in primary health-care use between treatment groups (appendix p 71).

32 serious adverse events were reported in 18 participants (15 events in seven [7%] of 107 participants in the quetiapine group and 17 events in 11 [11%] of 105 participants in the lithium group) (table 2). One patient in the lithium group had a serious adverse reaction (acute renal failure) and no SUSARs were reported in either group. The most common serious adverse event was overdose in both groups, occurring in three (3%) of 107 participants in the quetiapine group (seven events) and three (3%) of 105 participants in the lithium group (five events). All adverse events by group, as measured by the PRISE, are listed in the appendix (pp 99–100).

Costs, service use, and health-related quality of life data used for the economic analyses are in the appendix (pp 70–75). In the primary economic analysis, from an NHS and personal social services perspective, quetiapine was associated with lower cost and larger gain in QALYs, and therefore performed better than lithium (table 3). The cost-effectiveness plane showing NHS and personal social services cost and QALY differences at the 52-week follow-up is in the appendix (p 76). The plane indicated that there is a 92% chance that quetiapine results in lower costs and a larger gain in QALYs than lithium. The cost-effectiveness acceptability curve shows that the likelihood of quetiapine being cost-effective at the National Institute for Health and Care Excellence (NICE) willingness-to-pay threshold of £20 000 was 0.99 (appendix p 76). If the NHS was not willing to attach any monetary value to gains in QALYs (ie, a willingness-to-pay threshold of £0), the likelihood of quetiapine being most cost-effective was 0.92. Secondary analyses (adopting a societal perspective and using the QIDS-SR as the effectiveness outcome) and sensitivity analyses are in the appendix (pp 77–98). Although quetiapine seemed to be less cost-effective in these analyses than in the primary analysis, quetiapine remained the most cost-effective option according to the NICE willingness-to-pay threshold.

Discussion

We examined whether it is more clinically effective and cost-effective to prescribe quetiapine than lithium augmentation therapy for participants with treatment-resistant depression over the course of 12 months. We found a significantly greater reduction in one of the coprimary outcomes, self-reported depressive symptom severity over 12 months, in the quetiapine group than the lithium group, although the other coprimary outcome, time to trial medication discontinuation, showed no significant difference between groups. Quetiapine was more cost-effective than lithium from both an NHS and personal social services perspective and from a societal perspective. In secondary outcomes, the quetiapine group had less severe clinician-rated

symptoms of depression and less self-reported functional impairment at week 52, but not at week 8, and other secondary outcomes were not significantly different. Side-effects, as measured by the PRISE, and physical parameters (weight and blood pressure) were similar across groups.

Our findings suggest a moderate and clinically relevant benefit of quetiapine over lithium for long-term treatment of participants with treatment-resistant depression. It is important to note that we compared two active treatments, both of which have been shown to be effective compared with placebo, and found an apparent increasing difference between the two treatments over time. These results extend the previous finding that quetiapine is non-inferior to lithium over the short term and suggest superiority over the longer term.¹⁴

Binary response rates in this trial were modest and lower than those reported by Bauer and colleagues,¹⁴ which is probably due to differences in illness severity and trial design. Bauer and colleagues recruited participants with inadequate response to two or fewer antidepressant trials, whereas participants in the present trial had inadequate responses to two or more antidepressant trials, and 60% of participants had inadequate responses to three or more trials. The LQD trial is perhaps more comparable with the third and fourth steps of the STAR*D trial,³³ which investigated augmentation after inadequate response to two or three antidepressant trials and found remission rates closer to those reported in our trial. Regarding trial design, Bauer and colleagues randomly assigned participants directly to starting augmentation. In contrast, our trial was pragmatic; participants were randomly assigned to the decision to prescribe lithium or quetiapine, as would occur in the clinic, and subsequent initiation and continuation of treatment proceeded as per standard care. Thus, our trial included participants who were never prescribed or initiated the trial medication to which they were randomly assigned. We consider that inability to start treatment due to safety measures or other reasons, and less optimal treatment regimens not subject to rigid clinical trial direction, are inevitable in real-world augmentation treatment. As is often seen, such real-world treatment results in lower response rates than more traditional clinical trials. Nonetheless, the remission and response rates observed in this trial highlight the need for more effective treatment and management of treatment-resistant depression.

Although time to discontinuation of the trial medication did not significantly differ between groups, visual inspection of Kaplan-Meier discontinuation curves shows a more gradual decline in the quetiapine group than the lithium group in the first half of the trial period, which plateaued in the second half of the trial period. This might suggest there is a group of participants discontinuing relatively early, possibly due to side-effects, leaving a subsample of participants who perhaps persevere and perceive benefits from quetiapine, and

	Quetiapine (n=107)	Lithium (n=105)	Overall (n=212)
Serious adverse events, n	15	17	32
Type of serious adverse event, n (% of individuals experiencing the event)			
Overdose*	7 (3%)	5 (3%)	12 (3%)
Suicidal ideation	1 (1%)	1 (1%)	2 (1%)
Preparatory actions towards imminent suicidal behaviour	1 (1%)	1 (1%)	2 (1%)
Suicidal intention	1 (1%)	0	1 (1%)
Deliberate self-harm	1 (1%)	0	1 (1%)
Hiatus hernia	0	1 (1%)	1 (1%)
Gallstones	1 (1%)	0	1 (1%)
Acute renal failure	0	1 (1%)	1 (1%)
Acute kidney injury	0	1 (1%)	1 (1%)
Kidney stones	0	1 (1%)	1 (1%)
Pulmonary embolism	0	1 (1%)	1 (1%)
Methicillin-resistant <i>Staphylococcus aureus</i>	0	1 (1%)	1 (1%)
Migraine headache	1 (1%)	0	1 (1%)
Type 1 diabetes with ketoacidosis	0	1 (1%)	1 (1%)
Transient psychotic episode	1 (1%)	0	1 (1%)
Stomach cramps	1 (1%)	0	1 (1%)
Generalised tonic-clonic seizure	0	1 (1%)	1 (1%)
Multiple sclerosis	0	1 (1%)	1 (1%)
Cardiac arrest	0	1 (1%)	1 (1%)
Serious adverse events related to lithium or quetiapine add-on therapy, n (% of serious adverse events)			
Definitely related	0	0	0
Likely related	0	0	0
Possibly related	0	1 (6%)	1 (3%)
Unlikely related	7 (47%)	7 (41%)	14 (44%)
Not related	8 (53%)	9 (53%)	17 (53%)
Participants with serious adverse events, n (% of individuals experiencing any event)			
Overall	7 (7%)	11 (11%)	18 (9%)
Males	0	5 (5%)	5 (2%)
Females	7 (7%)	6 (6%)	13 (6%)

*Seven events occurred in three (3%) of 107 participants in the quetiapine group and five events occurred in three (3%) of 105 participants in the lithium group.

Table 2: Serious adverse events

	Cost (£)	QALYs	Incremental cost*	Incremental QALYs†	Incremental cost-effectiveness ratio	Incremental net health benefit‡
Lithium	3151.46	0.468	..	..	Dominated	..
Quetiapine	2706.77	0.540	-472.32	0.074	Dominating	0.097

QALY=quality-adjusted life-year. QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Rated. *Missing values were multiple imputed and the estimated difference was adjusted for treatment group, EQ-5D baseline index value, baseline cost of the same item, QIDS-SR baseline score, site, and number of failed antidepressant treatments. †Missing values were multiple imputed and the estimated difference was adjusted for EQ-5D baseline index value, QIDS-SR baseline score, site, and number of failed antidepressant treatments. ‡Assuming a willingness-to-pay threshold of £20 000 per QALY.

Table 3: Primary cost-effectiveness of lithium and quetiapine interventions from a National Health Service and personal social services perspective

thus remain on the medication longer term. In contrast, a sharper drop was observed early in the trial period in the lithium group, partly due to individuals not being suitable for lithium and never getting a prescription, followed by a gradual but continuous decline in the slope until the end of the trial, suggesting a steadier rate of discontinuations over 12 months and possibly poorer longer-term tolerability or efficacy. Future studies examining patient characteristics predictive of discontinuation of the trial medications might identify important factors to consider when choosing between treatments. We note that no weight gain was observed across time in the quetiapine group, in contrast to previous reports,³⁴ although this might be due to a relatively high mean baseline weight in this cohort.

The ITT analysis suggested that quetiapine was more effective than lithium in reducing depressive symptoms in pragmatic clinical practice; however, the superiority of quetiapine held even in the subset of participants who had a therapeutic treatment trial of the medication to which they were randomised. Although no significant difference was identified in time to discontinuation, the median time to discontinuation was the same in the two groups when those who had a therapeutic treatment trial of both trial medications were included, suggesting participants able to tolerate lithium and reach therapeutic serum levels might be more likely to remain on treatment.

The economic analysis suggested that quetiapine was associated with a lower cost to the NHS and better cost-effectiveness on an NHS, personal social services, and societal basis, both in terms of gains in QALYs and improvement in QIDS-SR scores. Although the probability of quetiapine being more cost-effective on a societal basis was reduced in comparison to the primary analysis, these results were robust to sensitivity analyses testing alternative assumptions regarding missing data, using generic drug costs, and testing the impact of the COVID-19 pandemic. Thus, our cost-effectiveness findings have clear implications for NHS treatment recommendations. A 2023 open-label study found higher remission rates with intranasal esketamine augmentation of antidepressants in treatment-resistant depression compared with extended-release quetiapine.³⁵ Although the benefits of esketamine were sustained over 32 weeks, esketamine is a more complex intervention than quetiapine, including lengthy and up to biweekly clinical interaction, often with a psychotherapeutic component. This might serve to enhance effectiveness but also increases the cost, and in 2022, NICE did not recommend the use of esketamine largely on the basis of uncertain cost-effectiveness.³⁶ Esketamine might be more clinically effective than quetiapine, but quetiapine is a less resource-intensive option that is more easily scalable in clinical services and, based on the LQD trial, cost-effective.

An important feature of the trial was the 52-week follow-up period. A 2019 meta-analysis of augmentation for treatment-resistant depression found that in

28 studies, the median follow-up duration was 6 weeks, and only two included a follow-up of 52 weeks, both of which compared an intervention (psychotherapy or lithium) against treatment as usual rather than a specified head-to-head comparator.³⁷ Treatment-resistant depression is frequently a chronic condition,¹⁵ and clinical guidelines recommend that participants responding to an acute trial of medication continue treatment for at least 9–12 months.⁹ Our long-term follow-up therefore provides a more relevant indication of comparative effectiveness in clinical practice. Relatedly, the primary outcome analysis used an area under the difference curve approach, using all available weekly QIDS-SR data for each participant, meaning that our results present a longitudinal view and reflect an overall reduction in depressive symptoms over the whole 12-month follow-up period, rather than simply a snapshot at a specific timepoint. The cumulative impact of this reduction in depression severity over 12 months might be more meaningful to participants.

A limitation of the trial was the substantial proportion of missing data for some of the secondary outcome measures. There was also slightly more missing data for the QIDS-SR and secondary outcome measures in the lithium group at weeks 26 and 52, although this was less apparent at week 8. As there was also a slightly higher rate of trial medication discontinuation and withdrawal from the trial in the lithium group, the missing data might represent less engagement in trial follow-up visits by these participants, introducing a possible detection bias. Alternatively, more engagement with the trial in the quetiapine group might have had differential effects on patients' depression. Another limitation is the reduced representation of non-White ethnic groups in the study sample. Finally, there was a chance imbalance in gender and employment between the two groups, with more males and higher unemployment in the lithium group than the quetiapine group. There is some evidence that unemployment is associated with poorer outcomes in depression,³⁸ so it is possible this imbalance contributed to better outcomes in the quetiapine group.

Although this trial and others suggest augmentation therapies are effective, few patients with treatment-resistant depression receive them.^{39,40} Augmentation is usually initiated in specialist mental health settings, and lithium in particular tends to be monitored in secondary rather than primary care.² However, only a minority of patients with treatment-resistant depression gain access to secondary care, and waiting lists are often long.³⁹ Methods to increase access to augmentation therapies are needed. This could include more primary care-based psychiatric services, together with education and training around prescribing and monitoring of augmentation for primary care physicians.

Our results suggest that in routine clinical practice, quetiapine is more beneficial than lithium in reducing

depressive symptoms and improving functioning in treatment-resistant depression. Our results also suggest quetiapine is more cost-effective, which has implications for NHS treatment recommendations. We would, however, caution against concluding that lithium is not a useful treatment for many patients with treatment-resistant depression. There is considerable evidence that lithium is an effective treatment, and epidemiological studies suggest lithium reduces suicidality and relapse with long-term use.^{41,42} Quetiapine and lithium might have different effects on some symptoms such as sleep, appetite, and anxiety, and therefore might be suitable for different presentations of depression. An important direction for future research will be to examine predictors of treatment response to establish whether there are additional factors that might guide treatment choice, and predictors of early discontinuation, which could potentially reduce the number of unsuccessful treatment trials.

LQD Study Group

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Contributors

AJC conceptualised the study, acquired resources and study funding, and was involved in the methodology, study supervision, data acquisition, and writing, reviewing, and editing the manuscript. JK-G was involved in data acquisition, project administration, and writing of the original draft. KG did formal analysis, and was involved in the methodology, and writing, reviewing, and editing the manuscript. ZZ and NY did the formal analysis, and were involved in writing, reviewing, and editing the manuscript. HJ was involved in the methodology, and writing, reviewing, and editing the manuscript. AC acquired resources, supervised the study, was involved in data acquisition, and was involved in writing, reviewing, and editing the manuscript. JRG acquired resources and study funding, supervised the study, was involved in data acquisition, and was involved in writing, reviewing, and editing the manuscript. DK acquired resources, supervised the study, was involved in data acquisition, and was involved in writing, reviewing, and editing the manuscript. RHM-W acquired resources and study funding, supervised the study, was involved in data acquisition, and was involved in writing, reviewing, and editing the manuscript. AHY acquired study funding, supervised the study, and was involved in writing, reviewing, and editing the manuscript. AB was involved in data acquisition, and writing, reviewing, and editing the manuscript. LM and RWT were involved in data acquisition, project administration, and writing, reviewing, and editing the manuscript. HT was involved in data acquisition, project administration, and writing, reviewing, and editing the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. KG and ZZ directly accessed and verified the data reported in this manuscript.

Declaration of interests

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Data sharing

Patient-level data will not be made publicly available. All data requests should be submitted to the corresponding author for consideration (anthony.cleare@kcl.ac.uk). Access to anonymised data might be granted following review by the Chief Investigator.

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