Comparative Effectiveness Research Trial for Antidepressant Incomplete and Nonresponders With Treatment Resistant Depression (ASCERTAIN-TRD):

Effect of Aripiprazole or Repetitive Transcranial Magnetic Stimulation Augmentation Versus Switching to the Antidepressant Venlafaxine on Quality of Life

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Abstract

Objective: This study compared the effects of augmenting antidepressants with aripiprazole or repetitive transcranial magnetic stimulation (rTMS) versus switching to venlafaxine XR/duloxetine on quality of life (QoL) among patients with treatment resistant depression (TRD).

Methods: In a predefined secondary analysis of a multisite, open-label, effectiveness trial, patients with TRD were randomly assigned to aripiprazole augmentation, rTMS augmentation, or switching to venlafaxine XR/duloxetine in a 1:1:1 ratio, and they were treated for 8 weeks. TRD was defined as an inadequate response to 2 or more antidepressant trials of adequate dose and duration, as defined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire. QoL was predefined as a key secondary end point for this study and assessed using the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF). A mixed-effects model with repeated measures was applied. This study was conducted from July 13, 2017, to December 22, 2021.

Results: Among 258 randomized participants with at least 1 postbaseline Q-LES-Q-SF measurement, augmentation with aripiprazole demonstrated statistically significant superiority over switching on the Q-LES-Q-SF ($P = .002$), while rTMS did not ($P = .326$). At end point, changes from baseline in the Q-LES-Q-SF scores were 10.61 (SE = 1.0) for aripiprazole augmentation, 11.59 (SE = 1.1) for rTMS augmentation, and 8.68 (SE = 0.9) for venlafaxine XR/duloxetine switch.

Conclusion: Augmentation with aripiprazole, but not rTMS, improved QoL significantly versus venlafaxine XR/duloxetine switch in TRD patients. However, a much smaller than expected sample size for the rTMS group may explain the lack of statistical significance rendering the latter finding of indeterminate nature.

Trial Registration: ClinicalTrials.gov identifier: NCT02977299.

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Major depressive disorder (MDD) is a prevalent, chronic, and highly disabling psychiatric disorder that significantly impairs quality of life (QoL).[1] By 2030, MDD is projected to become the leading cause of global disease burden, according to the World Health Organization.[2] Despite the availability of various antidepressants (ADs), approximately 30%–40% of MDD patients fail to achieve remission, and a substantial

Clinical Points

- This study compared aripiprazole or repetitive transcranial magnetic stimulation (rTMS) augmentation with switching to venlafaxine XR/duloxetine on quality of life (QoL) outcomes in treatment resistant depression patients.
- Aripiprazole or rTMS augmentation may offer a more effective strategy for improving QoL compared with standard antidepressant therapy alone.
- Patient-reported outcomes are crucial for understanding the impact of major depressive disorder and for assessing the effects of treatment interventions.

number of these patients fall into the category of treatment resistant depression (TRD).[3,4] TRD is defined as inadequate response after treatment with at least 2 different oral AD drugs taken at adequate doses for at least 6 weeks.[5,6]

QoL is a crucial measure of well-being and functioning in MDD. It is defined as "patients' own assessments of how they feel about what they have, how they are functioning, and their ability to derive pleasure from their life activities."[7] Therefore, within a biopsychosocial model, QoL is a broad, complex, and emergent concept that encompasses multiple psychosocial dimensions of life, such as physical health, psychological well-being, social relationships, satisfaction with life, living standards, and functionality. Patients with TRD experience a marked decline in QoL, often more severe than those suffering from chronic conditions.[8–12] QoL and functional impairments are particularly prolonged and severe in patients with TRD.[13–16]

Patient-reported outcomes (PROs), which consist of self-rating of symptom severity, functioning, and QoL, are increasingly utilized to assess patients with MDD. Self-perception of mental and physical health is a unique and key factor predicting clinical outcomes including functional recovery and remission.[17] QoL and functional outcomes have emerged as important treatment outcomes in MDD research.[13,18–21] Traditionally, treatments for depression have primarily targeted symptom remission.[22] However, achieving remission does not always translate to restoration of QoL and functioning.[23,24] Between 30% and 47% of MDD patients considered remitted from the clinician's perspective did not consider themselves to be in remission and continued to report some degree of QoL and functioning impairment.[24,25] Several studies have reported that only 50% of the variance in QoL is explained by depressive symptoms.[25,26] Thus, following treatment, many patients continue to live with symptoms that adversely affect their lives, suggesting that functional improvement may lag behind symptom improvement.[26–29] This represents an important aspect for MDD clinical trials: QoL and functional outcomes should be included in the outcome assessment.[13,30] The improvement of subjective QoL and functioning may be as important as the improvement of mood symptoms for patients with MDD and may be necessary to translate clinical response into restoration of psychosocial function.

To date, few AD trials have investigated QoL and functional outcomes in patients receiving guideline-recommended augmentation strategies following inadequate response to AD.[31–35]

In light of the importance of assessing and targeting functional outcomes in MDD, this effectiveness trial aimed to compare the effects on QoL outcome measures among TRD patients from randomized comparisons of augmentation with aripiprazole or augmentation with repetitive transcranial magnetic stimulation (rTMS) versus switching to the AD venlafaxine XR/duloxetine. In line with PCORI's emphasis on patient-centered outcomes, this study focused on outcomes that are highly relevant to patient's daily life. This trial showed a greater reduction in depressive symptoms following rTMS augmentation compared to switching to venlafaxine XR/duloxetine.[36] In the present study, we specifically analyzed QoL outcomes in the same trial.

METHODS

Study Design and Patients

We report a predefined analysis of QoL as a key secondary end point from a multisite, randomized, open-label, effectiveness trial comparing 3 treatment arms for MDD patients with TRD (ClinicalTrials.gov identifier: NCT02977299).[36] The study was conducted from July 13, 2017, to December 22, 2021. Outpatient subjects who experienced inadequate response to 2 or more ADs were randomized in a 1:1:1 fashion to one of 3 treatment arms: aripiprazole augmentation, rTMS augmentation, and venlafaxine XR/duloxetine, and patients were treated for 8 weeks. Inclusion and exclusion criteria were previously described in detail.[36]

Assessments

The short-form version of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) was predefined as a key secondary outcome measure for this study. The Q-LES-Q-SF is a 16-item validated patient-rated instrument and is among the most frequently used measures of QoL in psychopharmacology and clinical trials.[7,37] This tool was designed to measure a patient's satisfaction and enjoyment in different areas of daily functioning. The Q-LES-Q-SF's 16 self-report items evaluate overall enjoyment and satisfaction with physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual desire/interest/performance, economic status, vision, ability to get around physically, overall well-being, medications, and

contentment.[37] Items are rated on a 5-point Likert scale ("very poor," "poor," "fair," "good," "very good"), with higher scores indicating better enjoyment and satisfaction with life. The scoring of the Q-LES-Q-SF involves summing the first 14 items to yield a total score. The last 2 items about medication and overall contentment were added to the short form for clinical reasons and are scored separately.[37,38] The total score ranges from 14 to 70. The normal range that represents a community sample is 70–100, where the total score is expressed as a percentage based on the maximum total score of the items completed (0–100). Normal QoL is defined as Q-LES-Q-SF scores within 10% of community norms. Since community norm samples have an average Q-LES-Q-SF of 78.3 (SD, 11.3), a Q-LES-Q-SF score ≥70.47 is considered "within normal QoL."[34] The Q-LES-Q-SF was administered at baseline and at each postbaseline visit.

Statistical Analysis

The outcome for this study was predefined as the change from baseline in the Q-LES-Q-SF score. All efficacy analyses were conducted on the modified intent-to-treat dataset (mITT), where all patients with any postbaseline data were included. All tests were 2-sided. Because 2 different augmentation arms were each compared with switching to venlafaxine, we used a Bonferroni corrected α of 0.025 to assess statistical significance. Analyses were conducted using SAS V9.4. A mixed-effects model with repeated measures was used, including data from all patients with any postbaseline Q-LES-Q-SF data. This model included treatment group (augmentation versus switch) as the between-subjects factor, time (visit 1–7) as the within-subjects factor, and a group-by-time interaction term. The baseline measurement of the Q-LES-Q-SF score was included as a covariate. Determination of a significant treatment effect was based on the model's treatment group effect or treatment group-by-time interaction.[39] Hedges *g* effect sizes were computed for change from baseline to Week 8, comparing each augmentation group versus the switch group for each item in the Q-LES-Q-SF.

The percent of participants within normal range (Q-LES-Q-SF ≥70.47) was computed for the 235 participants with Q-LES-Q-SF scores at baseline and Week 8. The Q-LES-Q-SF total score is derived from the sum of scores from items 1 through 14. The range for Q-LES-Q-SF total scores is expressed in percentages. The percentage was calculated using the following formula: (Q-LES-Q-SF total score-14/(70-14))*100.[34]

RESULTS

A total of 278 participants were assigned to 1 of 3 treatment arms: aripiprazole n = 92; rTMS = 70; venlafaxine XR/duloxetine = 98. Among these 278 participants, 258 (92.8%) had at least 1 postbaseline Q-LES-Q-SF assessment and were eligible for the mITT analysis. Baseline demographic and clinical data are described in detail in the manuscript reporting results on the study primary outcome measure.[36] The baseline Q-LES-Q-SF scores (mean and standard deviation) were as follows: 33.88 (6.2) for aripiprazole augmentation, 33.98 (8.4) for rTMS augmentation, and 32.42 (7.7) for venlafaxine XR/duloxetine switch. Plots of baseline Q-LES-Q scores for each treatment group are shown in Supplementary Figures 1–3.

Change in Q-LES-Q-SF Scores: Aripiprazole Augmentation versus Switch to Venlafaxine XR/Duloxetine

A plot of change over time for each participant showed a linear change and did not indicate the presence of outliers. Examination of the goodness-of-fit statistic indicated that use of time without transformation and spatial powers correlated errors covariance structure produced the best fitting model. The treatment group main effect ($P = .002$) was statistically significant. The aripiprazole augmentation group showed higher scores, indicating a better outcome, than venlafaxine XR/duloxetine switch group. Model estimated mean (SE) change from baseline to week 8 in Q-LES-Q-SF scores for aripiprazole augmentation versus switching to venlafaxine XR/duloxetine was 10.61 (1.0) vs 8.68 (0.9) (Figure 1). The Hedges *g* for the total Q-LES-Q-SF score for rTMS aripiprazole augmentation versus switching was 0.2.

Change in Q-LES-Q-SF Scores: rTMS Augmentation versus Switch to Venlafaxine XR/Duloxetine

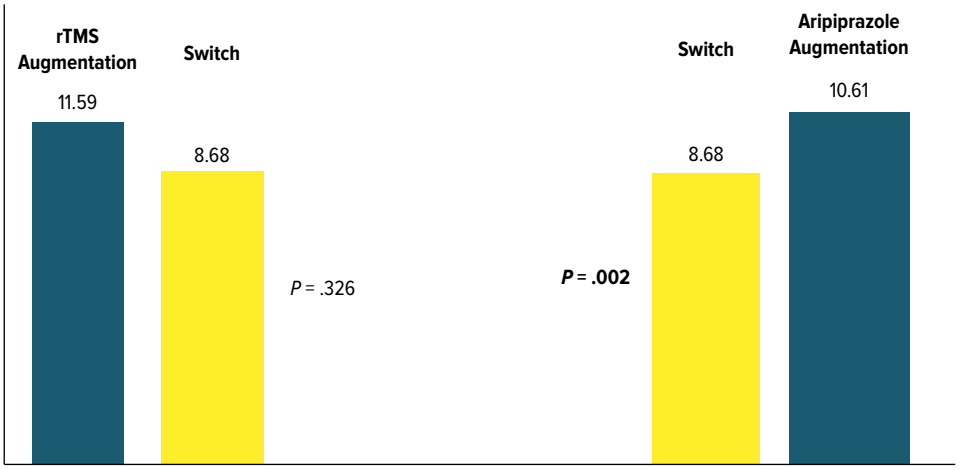
A plot of change over time for each participant showed a linear change and did not indicate the presence of outliers. Examination of the goodness-of-fit statistic indicated that use of time without transformation and spatial powers correlated errors covariance structure produced the best fitting model. The treatment group main effect was not statistically significant ($P = .326$). Model estimated mean (SE) changes from baseline to week 8 in Q-LES-Q-SF scores for rTMS augmentation vs switching to venlafaxine XR/duloxetine were 11.59 (1.1) versus 8.68 (0.9) (Figure 1). The Hedges *g* for the total Q-LES-Q-SF score for rTMS augmentation versus switching was 0.37.

The mean change from baseline on Q-LES-Q-SF items for aripiprazole augmentation, rTMS augmentation, and venlafaxine XR/duloxetine switch is illustrated in Supplementary Figure 4.

Proportions of Patients Scoring within Normal QoL Pre- and Posttreatment

Before and after treatment, the mean proportion of TRD patients scoring for a normal QoL was 0.43% and

Figure 1.
Model-Adjusted Change in Q-LES-Q-SF Scores[a]



[a]Alpha = 0.025.
Abbreviations: Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, rTMS = repetitive transcranial magnetic stimulation.

16.6%, respectively. The percentage of patients scoring for a normal QoL in the aripiprazole augmentation group at baseline and at week 8 were 0.00% and 13.10%, respectively. In the rTMS augmentation group, the percentage of patients scoring for a normal QoL at baseline and end point were 0.00% and 27.42%, respectively. In the venlafaxine XR/duloxetine switch group, the percentage of patients scoring for a normal QoL at baseline and end point were 1.12% and 12.36%, respectively.

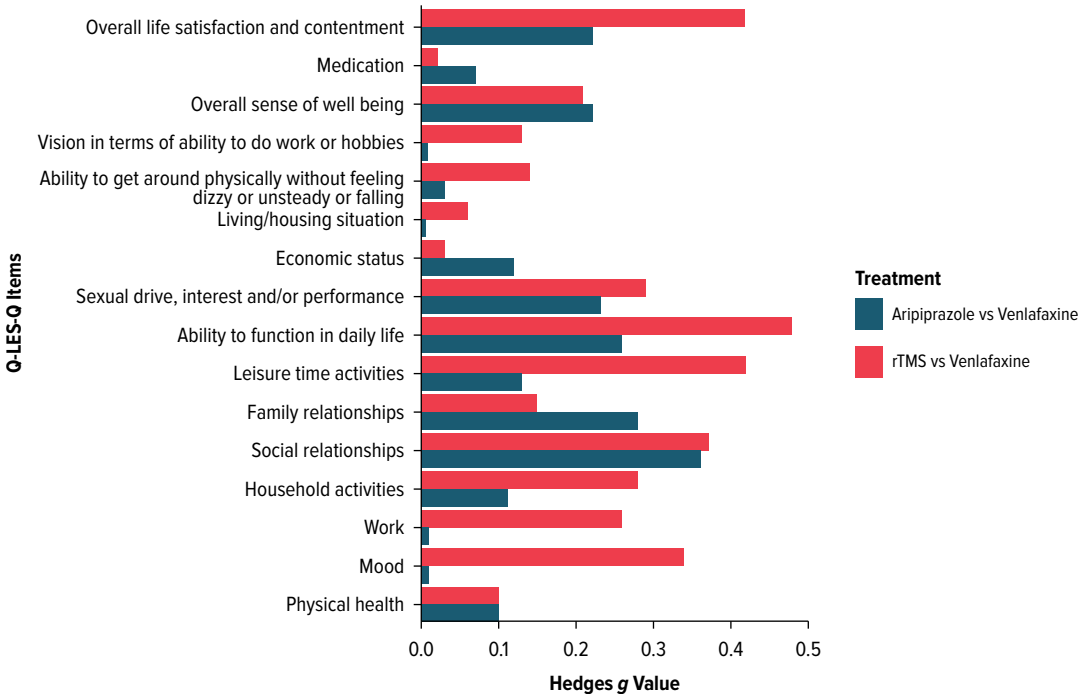
DISCUSSION

The present study is the first randomized effectiveness study designed to formally compare augmentation versus switching antidepressant on a patient-reported QoL outcome in outpatients with TRD.[36] With respect to QoL, our results demonstrate greater improvement in Q-LES-Q-SF scores following aripiprazole augmentation than switching to venlafaxine XR/duloxetine. This suggests that aripiprazole augmentation may offer a more effective strategy for improving QoL in patients with TRD. Conversely, while rTMS augmentation showed a greater reduction in depressive symptoms on the primary outcome than venlafaxine XR/duloxetine switch,[36] it did not reach a statistically significant difference in terms of QoL improvement. However, improvements in Q-LES-Q-SF outcome measure were numerically greater for rTMS augmentation than the other two groups (rTMS augmentation +11.59; aripiprazole augmentation +10.61; venlafaxine XR/duloxetine switch +8.68) while the error estimates were nearly identical (range 0.9–1.1). In fact, a numerically greater effect size (Hedges *g*) was seen for most Q-LES-Q-SF items for rTMS augmentation versus switching compared to aripiprazole augmentation versus switching (Figure 2). One factor that should be considered when interpreting these findings is the difference in mITT sample size between the two augmentation groups (only 70 patients were in the mITT sample for rTMS augmentation versus 91 for the aripiprazole sample). Notably, enrollment in the rTMS group was interrupted for nearly a year to minimize the chances of COVID spreading to patients and staff, since rTMS required many in-person visits. As a result, the rTMS group had a smaller number of participants. Therefore, it is possible that a significant treatment effect could have been detected on the Q-LES-Q-SF if we had been able to enroll more participants in the rTMS group. Hence, we view the results with respect to rTMS as hypothesis-generating rather than hypothesis testing.

To better understand the strength and clinical relevance of these findings, we have generated standard effect sizes for Q-LES-Q-SF items and total score. Utilizing conventions pertaining to the interpretation of the effect sizes across medicine[40] and considering that this is a comparison between 2 active treatments and not just placebo, as well as the global importance of the outcome measure, we would argue that anything greater than 0.2 is clinically relevant. Estimates for both augmentation treatments versus switch met this threshold, although the magnitude of the size effect is in the mild range in both cases. Alternatively, examining the Q-LES-Q as a

Figure 2.

Effect of Aripiprazole or rTMS Augmentation Versus Venlafaxine XR/Duloxetine Switch on Q-LES-Q-SF Items



Abbreviations: Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, rTMS = repetitive transcranial magnetic stimulation.

dichotomous outcome (ie, achieving scores within the normal range) can offer further insights with respect to QoL in TRD patients before and after treatment. Specifically, after rTMS treatment, approximately 27% of patients achieved QoL scores within the normal range, compared to 13% for aripiprazole augmentation and 12% venlafaxine XR/duloxetine switch. In contrast, following treatment with predominantly antidepressants (either alone or in combination) during the second level of Sequenced Treatment Alternatives to Relieve Depression (STAR*D),[22] Q-LES-Q scores reflecting normal function ranged between 6% (cognitive behavioral therapy augmentation) and 23.6% (bupropion augmentation), with a mean of approximately 20%. Of note, baseline scores within the normal range were similar between level 2 of STAR*D and ASCERTAIN and within the 0%–5% range. When contrasting these two trials, however, it is important to consider that the populations differ somewhat, with patients in level 2 of STAR*D having failed exactly 1 treatment (citalopram monotherapy), while patients in the ASCERTAIN-TRD study failed at least 2 treatments. The proportions of participants within the normal range for QoL at the end of level 3 and 4 in STAR*D are, approximately, 8% and 9%, respectively.[34] Therefore, this comparison would suggest that augmentation with atypical antipsychotics or rTMS may improve functional outcomes measured by QoL scales compared with standard antidepressant therapy, used either alone or in combination. As patient-reported outcomes are a valuable part of broader disease management, these results may inform on real-world effectiveness of treatments options with diverse side effect profiles, aiding patient-centered treatment decisions.

Several limitations of our study are worth mentioning. First, this was an open-label trial where, unlike raters, participants were not blinded to treatment assignment. Therefore, it is quite possible that patient attitudes, biases, preferences, and expectations might have influenced the results. Future confirmatory studies employing blinding are warranted. Additionally, enrollment in the rTMS group was interrupted for nearly a year to minimize the chances of COVID spreading to patients and staff, since rTMS required many in-person visits. As a result, the rTMS group had a smaller number of participants. Another limitation is that enrollment during the pre-COVID period was smaller than expected for two principal reasons: (1) the intensity of the rTMS treatment (daily visits for many weeks), being prohibitive for many patients, and (2) the criterion of no lifetime use of antipsychotic medications, which excluded many patients given the widespread use of these

medications among the target population. Future studies with larger sample sizes, more balanced allocation across treatment groups are warranted to fully assess the efficacy of rTMS in improving QoL. Another limitation is that the relatively short duration of treatment (8 weeks) may not have been sufficient to fully capture the impact of biological interventions on QoL measures. Longer-term studies are warranted. In addition, studies are designed to answer one main question, with MADRS as the primary outcomes in this case (case-in-point, results on the MADRS were more robust than for the Q-LES-Q). Even though QoL comparisons were defined in the protocol a priori as a secondary outcome measure, methodological alterations and adaptations would be required to the study design in order to test QoL as the primary outcome. Finally, whether our findings extend to specific subpopulations that were excluded in ASCERTAIN, such as adolescents or the elderly, remains unknown and should be addressed in future trials.

CONCLUSIONS

Augmentation with aripiprazole improved QoL significantly versus switching antidepressants in TRD patients. However, rTMS showed greater numerical improvements in Q-LES-Q-SF scale, compared to the other two groups, suggesting that a smaller sample size for the rTMS group may have contributed to the lack of statistically significant difference versus venlafaxine XR/duloxetine. Patient-reported outcomes are crucial for understanding the impact of MDD and for assessing the effects of treatment interventions, in both research and clinical settings. Future clinical trials of augmentation or switch strategies for MDD/TRD should increase the focus on QoL measures.

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From 2015–2021, Neuronetics Inc. donated TMS treatment supplies to a Northwestern University–funded clinical TMS trial for cancer survivors (25 patients) in which he was the principal investigator. **Dr Brawman-Mintzer** has received contract research grants from AgeneBio, Pfizer, Green Valley Pharmaceuticals, Avanir, Axsome Therapeutics, Takeda, DoD CDMRP, VA HSR&D, USC ATRI (NIA/NIH), UCSD ADCS (NIA/NIH), Lundbeck, Janssen, Shire, Eli Lilly, Biovail, UCB Pharma, Sanofi Aventis, AstraZeneca, Forest, Novartis, Merck, Bristol-Myers Squibb, and Wyeth-Ayerst; has received consultant fees from Janssen, Pfizer, AstraZeneca, and Forest; and has been on speakers bureaus for Pfizer, Janssen, AstraZeneca, and Forest. **Dr McCall** has received research support from Axon Medical Technologies and is a scientific advisor for Haleon, Idorsia, Liva Nova, and Carelon. **Dr Macaluso** has conducted clinical trials research as principal investigator for the following pharmaceutical companies over the last 12 months: AssureRx/Myriad, Avanir, Boehringer-Ingelheim, Electrocore, Janssen, Liva Nova, Merck, Neurocrine, Novartis, and Otsuka. 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He is a volunteer director on the board of directors of the British Columbia Schizophrenia Society. **Dr Carmody** has been a consultant for Alkermes. **Dr Fava**'s 3-year disclosures are as follows: research support from Acadia Pharmaceuticals; Aditum Bio Management Company, LLC; Allergan, Alkermes, Inc; Altimate Health Corporation; Alto Neuroscience, Inc; Ancora Bio, Inc; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals Inc; Axsome; Benckiser Pharmaceuticals, Inc.; BioClinica, Inc; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Centrexion Therapeutics Corporation; Cerecor; Cybin IRL Limited; Eliem Therapeutics LTD; Gate Neurosciences, Inc; GenOmind, LLC; Gentelon, LLC; Happify; Johnson & Johnson; Lundbeck Inc; Marinus Pharmaceuticals; Methylation Sciences, Inc; Millennium Pharmaceutics, Inc; Minerva Neurosciences; Neuralstem; Neurocrine Biosciences, Inc; NeuroRX Inc; Novaremed; Novartis; Otsuka; Pfizer; Premiere Research International; Praxis Precision Medicines; Protagenic Therapeutics, Inc; Relmada Therapeutics Inc; Reckitt; Shenox Pharmaceuticals; Stanley Medical Research Institute (SMRI); Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc; Xenon Pharmaceuticals, Inc; National Institute of Drug Abuse (NIDA); National Institutes of Health (NIH); National Institute of Mental Health (NIMH); and PCORI. Dr. Fava has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital, except for Sensorium Therapeutics. Speaking/publishing: lecture given at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/other financial options: equity holdings: Compellis; Neuromity; Psy Therapeutics; Sensorium Therapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Belvior; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd. All lifetime disclosures can be viewed online by navigating to: https://mghcme.org/faculty > Maurizio Fava, MD > View Bio > View Disclosures Here. **Dr Papakostas** has served as a consultant for Abbott Laboratories, Acadia Pharmaceuticals, Inc*, Alkermes, Inc, Almatica*, Alphasigma USA*, Inc, AstraZeneca PLC, Arrivo Bioventures-Sirtsei Phamaceuticals, Avanir Pharmaceuticals, Axsome Therapeutics*, Boehringer Ingelheim, Boston Pharmaceuticals, Inc*, Brainsway Ltd, Bristol-Myers Squibb Company, Cala Health*, Cephalon Inc, Dey Pharma, L.P., Eleusis health solutions ltd*, Eli Lilly Co, Genentech, Inc*, Genomind, Inc*, GlaxoSmithKline, Evotec AG, H. 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Supplementary Material

Article Title: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders with Treatment Resistant Depression (ASCERTAIN-TRD): Effect of Aripiprazole or Repetitive Transcranial Magnetic Stimulation Augmentation Versus Switching to the Antidepressant Venlafaxine on Quality of Life

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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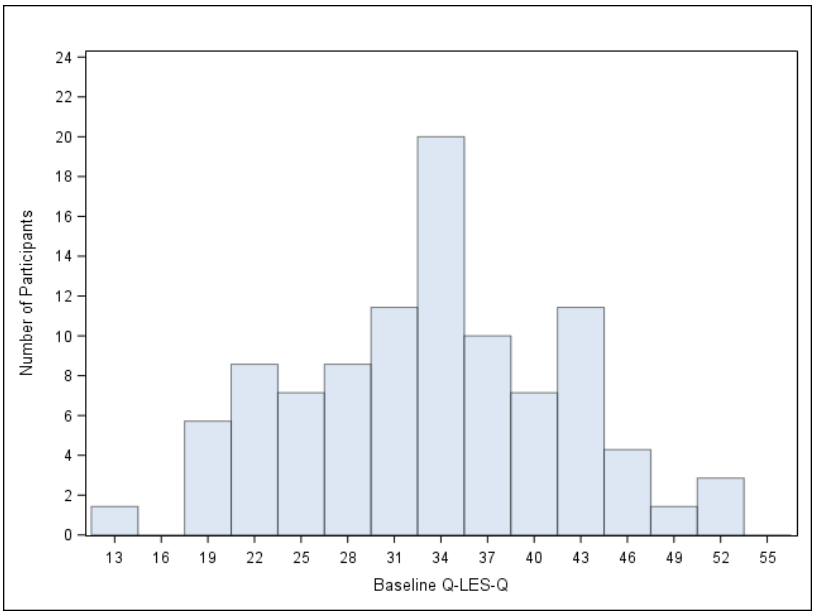
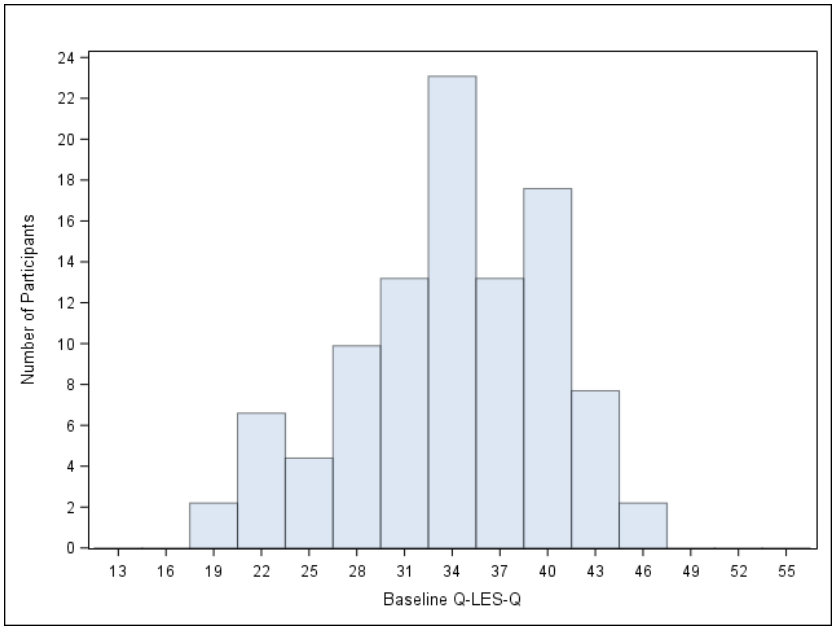
This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Materials

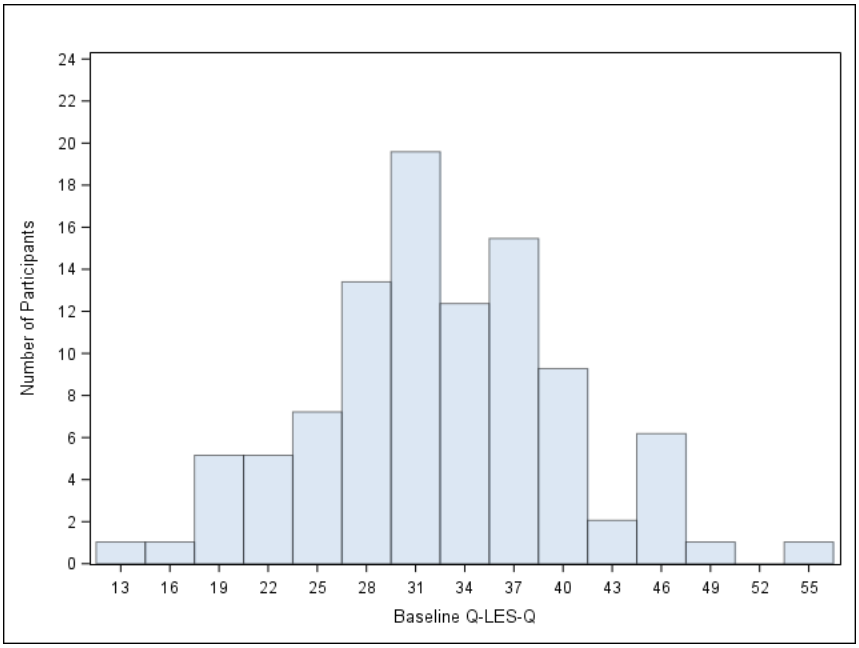
Supplementary Figure 1. Baseline Q-LES-Q scores for rTMS augmentation group.



Supplementary Figure 2. Baseline Q-LES-Q scores for aripiprazole augmentation group.



Supplementary Figure 3. Baseline Q-LES-Q scores for venlafaxine XR/duloxetine group.



Supplementary Figure 4. MMRM Analysis of Mean Change from Baseline on QLESQ Items for Aripiprazole Augmentation, rTMS Augmentation and Venlafaxine XR/Duloxetine Switch.