Supplementary Appendix

Supplement to: Lenze EJ, Mulsant BH, Roose SP, et al. Antidepressant augmentation versus switch in treatment-resistant geriatric depression. N Engl J Med 2023;388:1067-79. DOI: 10.1056/NEJMoa2204462

This appendix has been provided by the authors to give readers additional information about the work.

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Principal Investigators and Recruitment Sites

Included below are the Principal Investigators and corresponding institutional affiliation. Many additional Co-Investigators and research staff members were involved in the trial.

Principal Investigator	Site
Eric J. Lenze, MD	Washington University (Coordinating Site)
Benoit H. Mulsant, MD	University of Toronto
Helen Lavretsky, MD	University of California, Los Angeles
Steven P. Roose, MD, Patrick Brown, PhD	Columbia University
Charles F. Reynolds, III, MD, Jordan Karp, MD, Marie Anne Gebara, MD	University of Pittsburgh

Patients were recruited via a variety of mechanisms including primary care provider referrals triggered by office advertisements, outreach from the study team, and electronic medical record automated alerts, referrals from psychiatrists, and self-referrals that responded to print, radio, and social media advertising. Below is a listing of each research site's recruitment sites.

Columbia University

- Adult and Late Life Depression Clinic
- Associated in Internal Medicine Main
- Associates in Internal Medicine East
- Broadway Clinic
- Depression Evaluation Services Riverside Drive
- Farrell Clinic
- Memory Disorders Clinic at NY State Psychiatric Institute
- Metropolitan Center for Mental Health
- Rangel Clinic
- Washington Heights Family Health Clinic

UCLA

- Behavioral Health Associates and Behavioral Health Clinic at UCLA
- Late Life Wellness Group
- The Stewart and Lynda Resnick Neuropsychiatric Hospital at UCLA
- UCLA Geriatric Evaluation Clinic
- UCLA Geriatric Medicine Clinic
- VA West Los Angeles Geripsych Clinic
- VA West Los Angeles Mood Clinic

University of Pittsburgh

- Absolute Primary Care
- Benedum Geriatric Center
- BEST
- Craig Medical Associates
- GIMO
- Health Care Associates
- Mon Yough
- Shadyside Senior Care
- Solano Practice

Washington University

- Alton Multispecialists
- Anderson Medical Group
- BJC Medical Group
- COMTREA
- Esse Health
- Family Care Health Center
- Mercy Clinic Internal Medicine
- Psych Care Consultants
- St. Luke's Medical Group
- Washington University Physicians

University of Toronto

- Centre for Addiction and Mental Health
- St. Michael's Hospital
- Sunnybrook Health Sciences Centre
- University Health Network

Methods: Inclusion/Exclusion Criteria

The following was used for trial inclusion and exclusion criteria.

<table>
<tr><th colspan="2">Eligibility Criteria for Step 1 and Step 2</th></tr>
<tr><th>Inclusion Criteria</th><th>Exclusion Criteria</th></tr>
<tr><td rowspan="5">Men and women aged 60 and older
Current Major Depressive Disorder (MDD), single or recurrent, as diagnosed by DSM-5 criteria
Failure to respond adequately to two or more antidepressant treatment trials of recommended dose and length (approximately 12 weeks)
PHQ-9 score of 10 or higher (criteria was increased from 6 after the first 18 months of enrollment)</td><td>Inability to provide informed consent
Dementia, as defined by Short Blessed ≥ 10 and/or clinical evidence of dementia.
Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms.
High risk for suicide (e.g. active SI and or current/recent intent or plan) and unable to be managed safely in the clinical trial, such as unwilling to be hospitalized).
Contraindication to proposed study medications, as determined by study physician including history of intolerance or non-response to study medications.
Non-correctable, clinically significant sensory impairment (e.g., cannot hear well enough to cooperate with interview)
Unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, hyperlipidemia, or cerebrovascular or cardiovascular risk factors that are not under medical management (Determined based on information from the patient’s personal physician and study physician’s clinical judgement)
Moderate to severe substance or alcohol use disorder, as determined by study physician.</td></tr>
<tr><td>Additional Step 1 Exclusion Criteria*</td></tr>
<tr><td>Seizure disorder
Parkinson’s Disease</td></tr>
<tr><td>Additional Step 2 Exclusion Criteria</td></tr>
<tr><td>QTc prolongation or Wide QRS on EKG
Ischemic Heart Disease (e.g., prior MI, stent, or bypass)
Acute or chronic renal insufficiency</td></tr>
</table>

*Step 1 medications are contraindicated in these conditions. In the event participants were diagnosed with these conditions, they were considered ineligible for Step 1 participation. During the first 18 months of enrollment, these subjects were considered eligible for direct Step 2 participation if all other inclusion/exclusion criterion were met.

Methods: Summary of Outcomes

Below we summarize measurement and analysis of primary and secondary outcomes for the acute phase. Additional information is included in the Statistical Analysis Plan.

Outcome	Primary vs Secondary	Measurement	Range	Interpretation	Endpoint	Analysis Approach
Effectiveness Outcomes						
Psychological Well-Being	Primary (patient-centered)	Average of 2 NIH Toolbox Psychological Well-being subscales (Positive Affect and Life Satisfaction)	Standardized scores; T-score metric (population mean=50)	Higher scores indicate greater psychological well-being	Acute phase Step end (week 10)	Step 1: repeated measures ANOVA w/Hochberg Step-down procedure to determine significance for pairwise comparisons[1] Step 2 : repeated measures ANOVA
Remission from Depression[2]	Secondary (clinician-focused)	MADRS[3]	0 to 60	Higher scores indicate greater depressive symptom severity	Acute phase Step end (week 10)	Generalized linear models with poisson link function
Changes in Depressive Symptoms	Secondary	MADRS	0 to 60	Higher scores indicate greater depressive symptom severity	Acute phase Step end (week 10)	Mixed model, repeated measures ANOVA
Social Participation	Secondary	PROMIS Ability to Participate in Social Roles and Activities Computer Adaptive Test v2.0[4]	Standardized scores; T-score metric (mean=50, SD=10)	Higher scores indicate greater social participation	Acute phase Step end (week 10)	Mixed model, repeated measures ANOVA
Physical Function	Secondary	PROMIS Physical Function Computer Adaptive Test v2.0[5]	Standardized scores; T-score metric (mean=50, SD=10)	Higher scores indicate greater physical function	Acute phase Step end (week 10)	Mixed model, repeated measures ANOVA

Outcome	Primary vs Secondary	Measurement	Range	Interpretation	Endpoint	Analysis Approach
Safety Outcomes						
SAEs	Primary	Occurrence Date/Self-Report	Count of SAEs, severity, relatedness to intervention	More SAEs, higher severity, relatedness, greater safety concern	February 2017-December 2021	Proportional hazard model with repeated events; rate (number of SAEs/number of participants in treatment arm)
Falls	Primary	Self-Report	0, 1, 2, ≥3 falls	More falls, greater safety concern	Bi-Weekly study call/visits during acute phase[6]	Generalized mixed linear repeated measures model with Poisson link function; rate (number of falls/number of participants in treatment arm)
Injurious Falls	Secondary	Self-Report	Positive vs negative endorsement of injurious fall (yes/no)	More injurious falls, greater safety concern	Bi-Weekly study call/visits during acute phase[6]	Generalized mixed linear repeated measures model with simple logistic link function
AEs	Safety Reporting	Occurrence Date/Self-Report	Count of AEs, severity	More AEs, higher severity, greater safety concern	February 2017-December 2021	Rate (number of specific AE/number of participants in treatment arm)

Abbreviations: MADRS, Montgomery-Asberg Depression Scale; NIH, National Institutes of Health; SD: standard deviation; ANOVA, Analysis of Variance; PROMIS, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event

[1] For the Hochberg Step-down procedure, if the comparison with the lowest p-value < 0.05/3=0.017, it is significant. If the second lowest p-value is < 0.05/2=0.025, then it also will be significant and if the third p-value is < 0.05 then it also will be significant. The Hochberg Step-down procedure was not used for Step 2. Step 2 was considered a separate analysis from Step 1.

[2] Remission was defined as a final MADRS $\leq$ 10 or if MADRS unavailable, PHQ9 ≤5.

[3] Measured by 7 blinded raters.

[4] This scale evaluates self-reported ability to participate in social activities and roles.

[5] This scale evaluates physical capability based on self-reported functioning (e.g. dexterity, mobility, walking, etc.) and ability to perform instrumental activities of daily living.

[6] Conducted by independent, non-blinded rater.

Methods: Re-calculated Power to Detect Effect Size of the Benefits and Risks of Antidepressants

As described in Methods, the sample size was recalculated based on actual recruitment in December 2019. As a conservative method for computing the detectable effect size, we used simple t-tests for comparing change scores between groups. The research on minimally clinically relevant changes for Toolbox or PROMIS measures suggests that they are between 2-3 T-score points (personal communication, David Cella, PI of PROMIS Statistical Center). The table below shows that we had power > 0.80 to detect clinically relevant changes. For proportional outcomes, we used the conservative approach of a simple comparison between proportions for remission. Difference of 10 percentage points around a remission rate of 40% are generally considered clinically meaningful. Serious Adverse Events was a time to event analysis, but reported in Results as a rate (i.e., number of SAEs/number of patients in acute treatment arm) to translate into clinically understandable terms. Falls power analysis and data analytic techniques were based on proportion of biweekly assessments in which a fall was reported. However, we also reported fall data in Results as a fall rate (i.e., number of falls/number of patients in acute treatment arm) to translate into a clinically understandable terms. Secondary tests of effectiveness examined changes in other aspects of quality of life: physical function, social participation, and changes in depressive symptoms (i.e., MADRS scores). Detectable differences for these endpoints are included below.

Power to Detect Effect Size of the Benefits and Risks of Antidepressants Based on Recalculated Sample Size

	Step 1 Effect[1]		Step 2 Effect[2]	
Power	**.8**	**.9**	**.8**	**.9**
Toolbox Psychological Well-being[3]	2.6	3.0	2.9	3.3
PROMIS Physical Function[3]	2.6	3.0	2.9	3.3
PROMIS Social Participation[3]	2.6	3.0	2.9	3.3
Remission[4]	16.3%	18.5%	17.7%	20.4%
Serious Adverse Events[5]	9.1%	10.8%	10.2%	12.3%
Falls[6]	14.5%	16.7%	15.9%	18.6%
Fall-related injuries[7]	9.1%	10.8%	10.2%	12.3%
MADRS[8]	3.0	3.4	3.2	3.7

[1] n=195 each for 3 groups, p=.05/3

[2] n=124 each for 2 groups, p=.05

[3] Points on T-score; sd=8 beginning and end of phase, r=0.5 between scores

[4] Difference in proportion remitting, around a 40% remitting point

[5] Increase in proportion experiencing an SAE, around a 4% baseline rate

[6] Increase in proportion experiencing a fall, around a 20% baseline rate

[7] Increase in proportion experiencing an injurious fall, around a 4% baseline rate

[8] Scale point change, sd=9 beginning and end of phase, r=0.5 between scores

Methods: Benjamini-Hochberg Procedure Overview and Interpretation

For Step 1 only, a repeated measure ANOVA was used to test the hypothesis for the patient-centered primary outcome, psychological well-being. The ANOVA was based on age (<70 vs >70), time (baseline, end of Active phase of Step 1), primary care vs specialty care, clinic and treatment group (augment-aripiprazole, augment-bupropion, switch-bupropion). Time*treatment group contrasts were used to compare the changes across pairs of treatment groups (e.g., augment-aripiprazole versus augment-bupropion). These tests of significance were conducted using the Benjamini Hochberg Step-down procedure. A primary purpose of the Benjamini-Hochberg Step-down procedure is to control or minimize the risk for a 'false discovery.'

We pre-specified the following:

- If the comparison with the lowest p-value < 0.05/3=0.017, it is significant.
- If the second lowest p-value is also < 0.05/2=0.025, then it also will be significant
- If the third lowest p-value is < 0.05, then it also will be significant

To illustrate application of the Benjamini-Hochberg procedure, results from Psychological Wellbeing hypothesis-testing are provided below.

Comparison	**p-value**	**Rank (lowest p-value=1, largest p-value=3)**	**Is it significant?**
Augment-aripiprazole vs switch-bupropion	0.014	1	Yes (0.014 < 0.017)
Augment-bupropion vs switch-bupropion	0.049	2	No (0.049 > 0.025)
Augment-aripiprazole vs augment-bupropion	0.66	3	No (0.66 > 0.05)

Based on these pre-specified p-values, only one of the comparisons is significant: the lowest p-value was observed between augment-aripiprazole and switch-bupropion treatment groups (p=0.014). We pre-specified that if the comparison with the lowest p-value was less than 0.05/3=0.017, it would be considered significant. Since the p-value is less than 0.017, it is significant. The second lowest p-value (0.049) was observed in the comparison of the augment-bupropion to the switch-bupropion group. We pre-specified that the second lowest p-value would be considered significant if it was less than 0.05/2=0.025. Since 0.049 is greater than 0.025, this comparison is not considered significant. The third lowest p-value was observed between the augment-aripiprazole and augment-bupropion group. This comparison is also not considered significant as 0.66 is greater than 0.05, the pre-specified significance level for the comparison with the third lowest p-value.

Methods: Decision Support, Measurement-Based Care, and Prescribing Instructions Used in Trial

The OPTIMUM study's pragmatic, comparative effectiveness design allowed research participants to continue to receive ongoing care, management, and prescriptions from their own physicians. Once randomized to the well-established, evidence-based, standard of care treatment, the research team assessed participants for symptoms and tolerability by phone every two weeks during the acute treatment phase (approximately 10 weeks). The research team communicated recommendations for medication dosing and changes to the treating clinician; the treating clinician was permitted to override or ignore medication recommendations.

- Dose adjustment was done by the treating clinician with support from the OPTIMUM research team. The OPTIMUM research team made dose adjustment recommendations using the following criteria:
    - If PHQ-9 score was 6 or greater and side-effects were absent or well-tolerated, the team recommended an increase in the dose, until reaching the maximum dosage.
    - If PHQ-9 score was 5 or less or side-effects were significant enough that participant could not tolerate a dose increase, the team recommended keeping the dose the same.
    - If side-effects were significant enough that the participant needed a dose decrease, the team recommended decreasing dose back to the previous dosage.
    - If side-effects were intolerable such that the participant needed a medication change, the team recommended ending the step and proceeding to the next step (or ending study treatment if already in Step 2).
- Clinicians and patients had flexibility: they could decide to exit Step 1 or Step 2 treatment early (e.g., due to tolerability issues). Clinicians were allowed to co-prescribe other medications, as well.
- During decision support calls, the research team also asked participants about their study medication adherence. If participants missed doses, brief counselling about adherence, including the importance of 100% adherence, and steps to resolving barriers to adherence, were discussed.

In this step-wise design, participants were randomized 1:1:1 to a Step 1 medication strategy: augment-aripiprazole, augment-bupropion, or switch-bupropion. Participants whose depression had not remitted at the end of Step 1 or were ineligible for Step 1, were randomized 1:1 to a Step 2 medication strategy: augment-lithium or switch-nortriptyline. Bupropion, aripiprazole, and nortriptyline were used within their FDA-indicated population (adults), disease (major depressive episode), dosage, and route of administration (PO). Lithium was used within the FDA-indicated population (adults), dosage, and route of administration (PO), but for an off-label indication (it is approved for bipolar disorder but not major depression, although it has been shown efficacious in depression in previous trials). Prescribing information for each medication strategy is included below. This was used by the research team for making recommendations to the treating clinicians.

Aripiprazole Augmentation Prescribing Information

Starting Dose	2.5 mg (or 2mg, at prescriber's discretion)
Maximum Dose	15 mg
Titration	Study team recommended increases approximately every two weeks (5 mg, 7.5 mg, 10 mg, 15 mg) based on symptoms and tolerability.

Bupropion Switch and Augmentation Prescribing Information

Starting Dose	150 mg
Maximum Dose	450 mg
Titration	Study team recommended increase to 300 mg after approximately two to four weeks based on symptoms and tolerability.

Lithium Augmentation Prescribing Information

Starting Dose	300 mg QHS (150 mg QHS for patients with impaired renal function, heart failure, or who were taking medications known to interact with lithium)
Maximum Dose	Adjusted per blood level up to 1200* mg *Study team assessed adherence and review of blood level lab values with patient prior to increasing Lithium higher than 600 mg
Titration	Checked blood level ~1 week after initiating. Adjusted dosage linearly to target 0.6 mEq/L. Rechecked level 1-2 weeks later. Adjusted dose as needed to keep participant in 0.4-0.8 mEq/L window. In some cases, levels outside of this range were considered acceptable based upon Principal Investigator discretion.

Nortriptyline Switch Prescribing Information

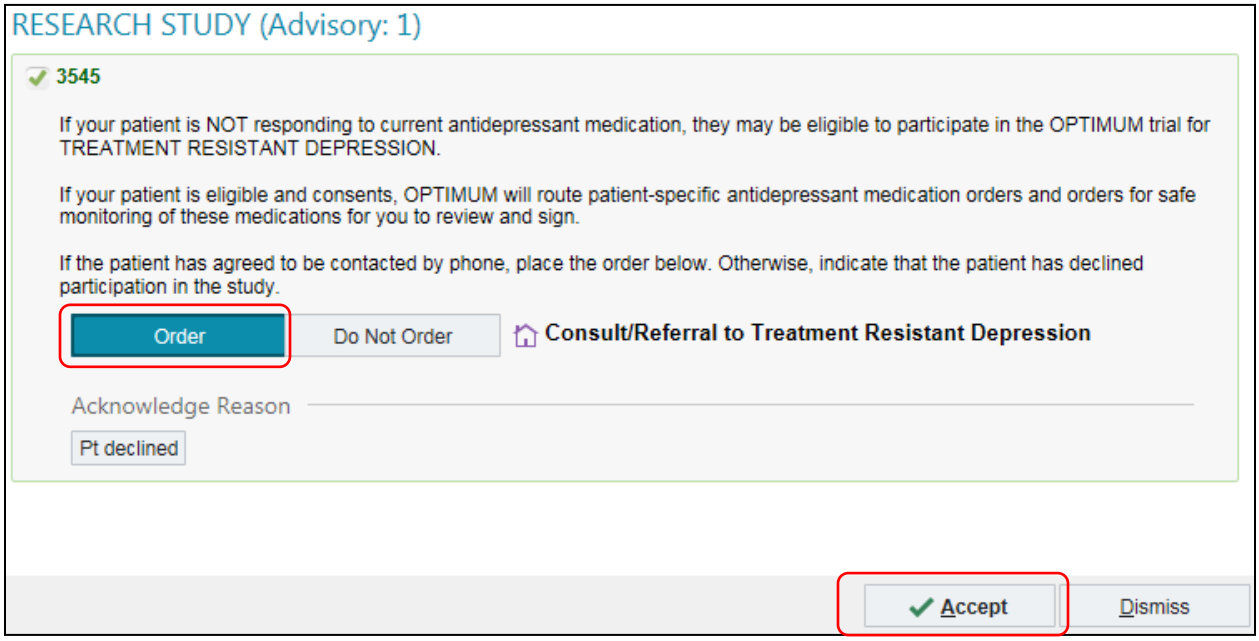
Starting Dose	25 mg
Maximum Dose	Adjusted per blood level up to 150 mg
Titration	Study team recommended increasing by 25 mg approximately every 5-7 days until reaching target dose of 1mg per kg of body weight. Measured blood level ~5-7 days after reaching target dose and adjusted dose accordingly, targeting therapeutic range of 80-120 ng/ml. In some cases, levels outside of this range were considered acceptable based upon Principal Investigator discretion.

Methods: Guidelines Used to Transition Patients from Step 1 Medications to Step 2 Medications
Patients who failed to remit in Step 1 were randomly assigned on a 1:1 ratio to switch-nortriptyline or augment-lithium. Below we summarize guidelines used in transitioning participants from Step 1 medications to Step 2 medications.

Step 1 Randomization Assignment	**Step 2**	
	Switch-Nortriptyline	**Augment-Lithium**
Augment-Aripiprazole (antidepressant medication + Aripiprazole)	(1) Discontinue Aripiprazole (2) Discontinue or taper antidepressant medication (3) Start Nortriptyline	(1) Discontinue Aripiprazole (2) Start Lithium
Augment-Bupropion (antidepressant medication + Bupropion	(1) Discontinue Bupropion (2) Discontinue or taper antidepressant medication (3) Start Nortriptyline	(1) Patient and their clinician choose whether to discontinue Bupropion or discontinue or taper as antidepressant medication (2) Start Lithium
Switch-Bupropion	(1) Discontinue Bupropion (2) Start Nortriptyline	(1) Start Lithium

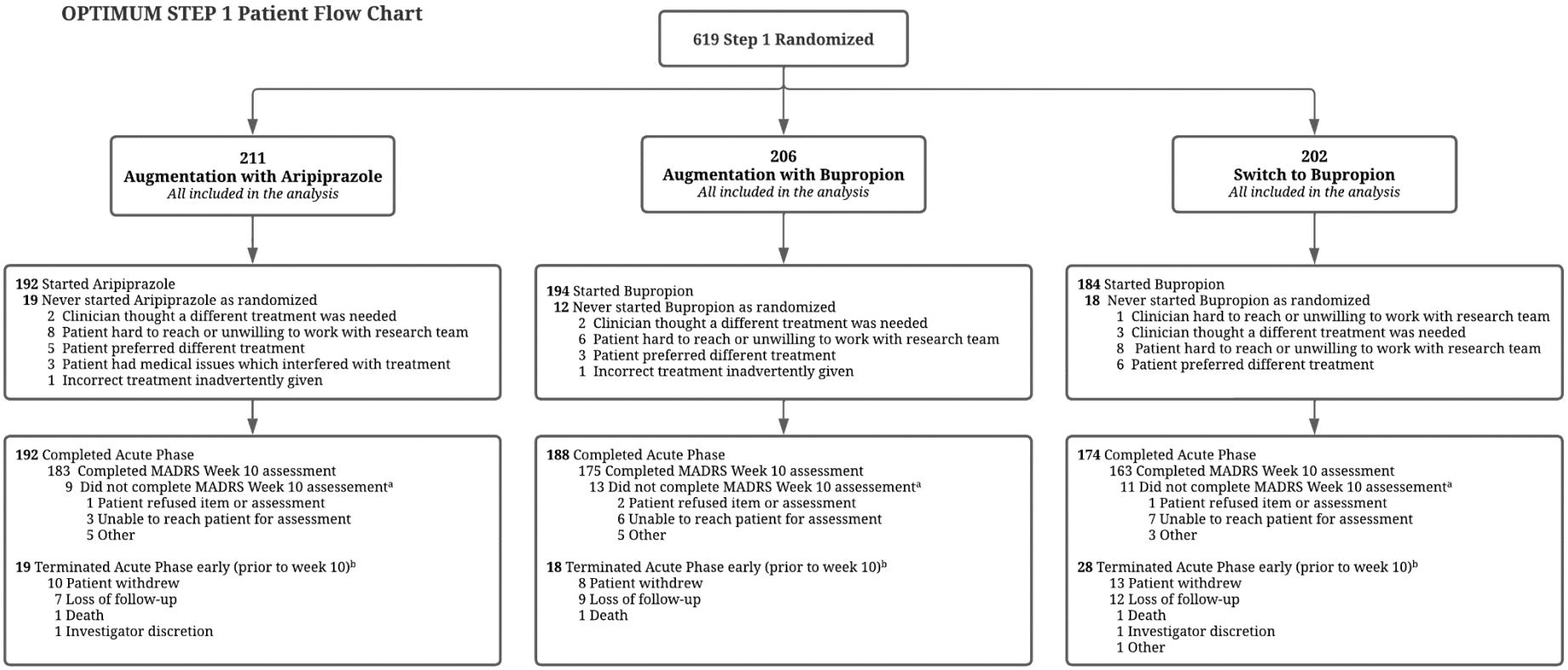
* Some antidepressant medications can be discontinued (e.g., fluoxetine) and most need to be tapered either rapidly (e.g., sertraline) or slowly (e.g., paroxetine or venlafaxine)

Figure S1. Best Practice Alert (BPA) Using Electronic Medical Record Decision Tool



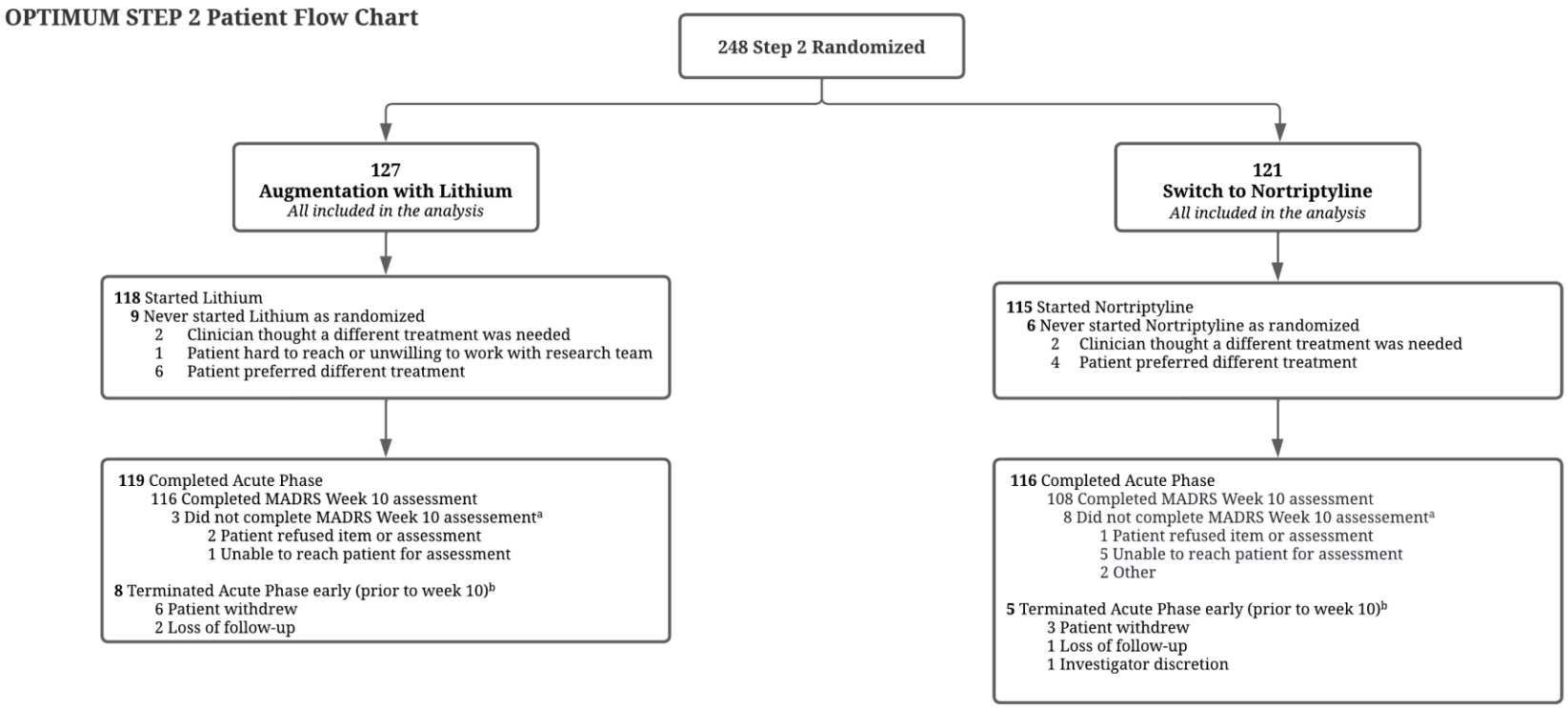
At the time of the office visit, the BPA alerted physicians if the patient may qualify for the study. This provided the physician an opportunity to ask the patient if they were interested in participating in the study, and to obtain permission for the study team to contact the patient. If the patient agreed to be part of the study, the provider selected 'Order' and then 'Accept' to place order for referral. The order then displayed on the order entry for the provider to sign and once signed, study coordinators received a notification of the order in their electronic medical record 'In-Basket.' This prompted the study coordinator to contact the patient, allowing for efficient and timely follow-up.

Figure S2. Step 1 Detailed Patient Flow Chart



[a] When MADRS at week 10 assessment was not completed, PHQ-9 at week 10 (if available) was used to define the remission status. (Augmentation with aripiprazole: 9; Augmentation with Bupropion: 12, Switch to Bupropion: 9)
When both MADRS and PHQ-9 at week 10 were not available, the remission status was defined as "non-remitter".(Augmentation with aripiprazole: 0; Augmentation with Bupropion: 1, Switch to Bupropion: 2)
[b] Included in the analysis and treated as "non-remitter" with the respect to the primary effectiveness analysis.

Figure S3. Step 2 Detailed Patient Flow Chart



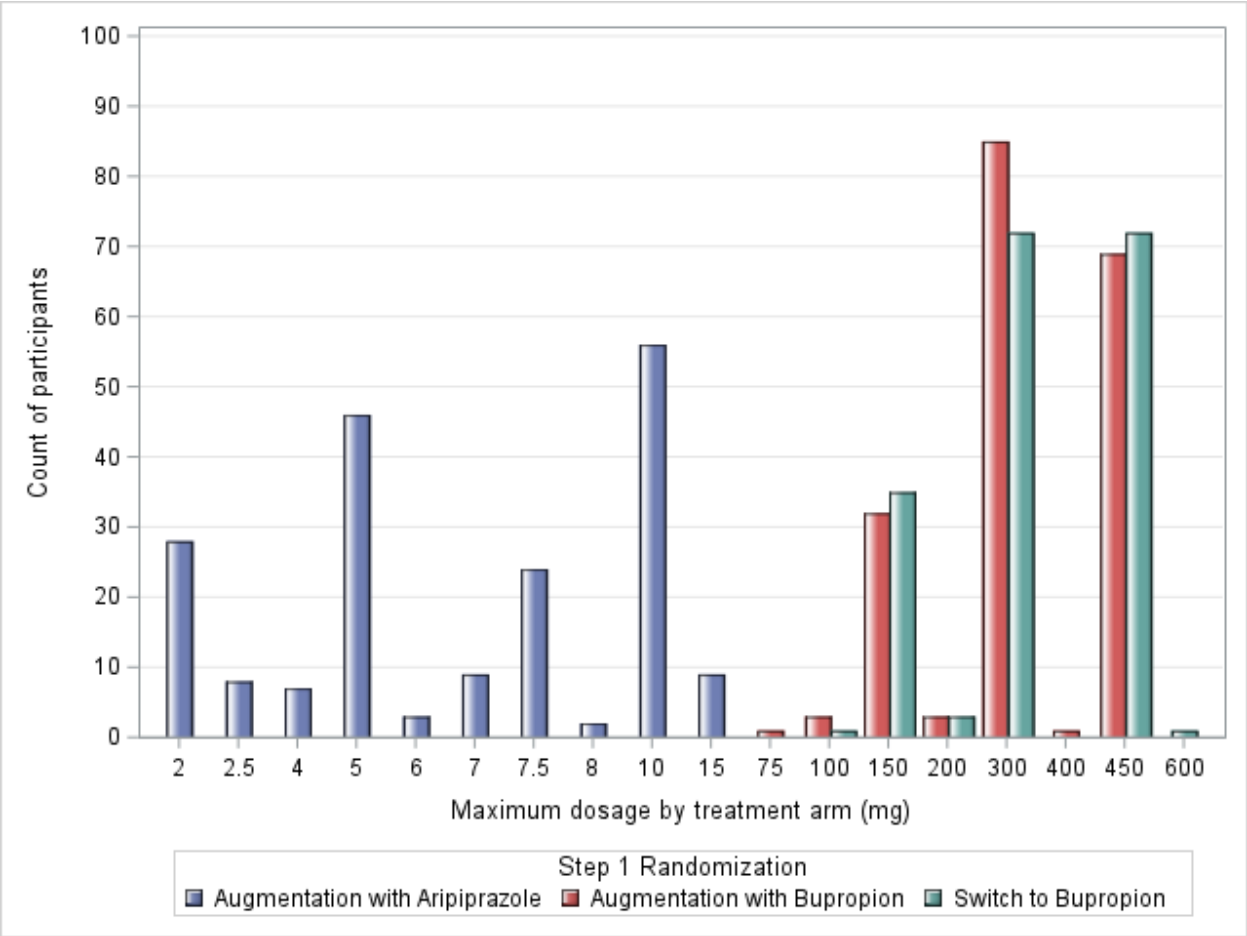
[a] When MADRS at week 10 assessment was not completed, PHQ-9 at week 10 (if available) was used to define the remission status. (Augmentation with lithium: 1, Switch to nortriptyline: 2) When both MADRS and PHQ-9 at week 10 were not available, the remission status was defined as "non-remitter". (Augmentation with lithium: 2, Switch to nortriptyline: 6)

[b] Included in the analysis and treated as "non-remitter" with the respect to the primary effectiveness analysis.

Figure S4: Highest Dosage of Trial Medications Reached by Step 1 and Step 2 Participants

The Prescribing Instructions on pages 10-11 of this Appendix describe starting and maximum dosages for each of the trial medications (e.g., aripiprazole, bupropion, etc.), as well as the titration strategies. Symptoms and tolerability of trial medications were assessed by phone every two weeks during the acute treatment phase. As a pragmatic trial, the treating clinician could decide to follow or override recommendations for dosage change. The maximum dose of trial medications was not reached for all participants due to symptom and tolerability concerns. The histograms below show the range of maximum dosages of the trial medications; y-axis shows the number of participants that reached these maximum dosages.

Figure S4a. Maximum Study Medication Dose Reached By Step 1 Participants



*In 2 instances, the patient mistakenly took 300mg two times daily instead of once daily. This was only for a short duration in both cases (3-4 days).

**Since medications were administered in real-world care settings, many patients opted to start at a 2 mg pill (rather than 2.5mg), which was allowable per the pragmatic framework of this study.

Figure S4b. Maximum Study Medication Dose Reached by Step 2 Participants

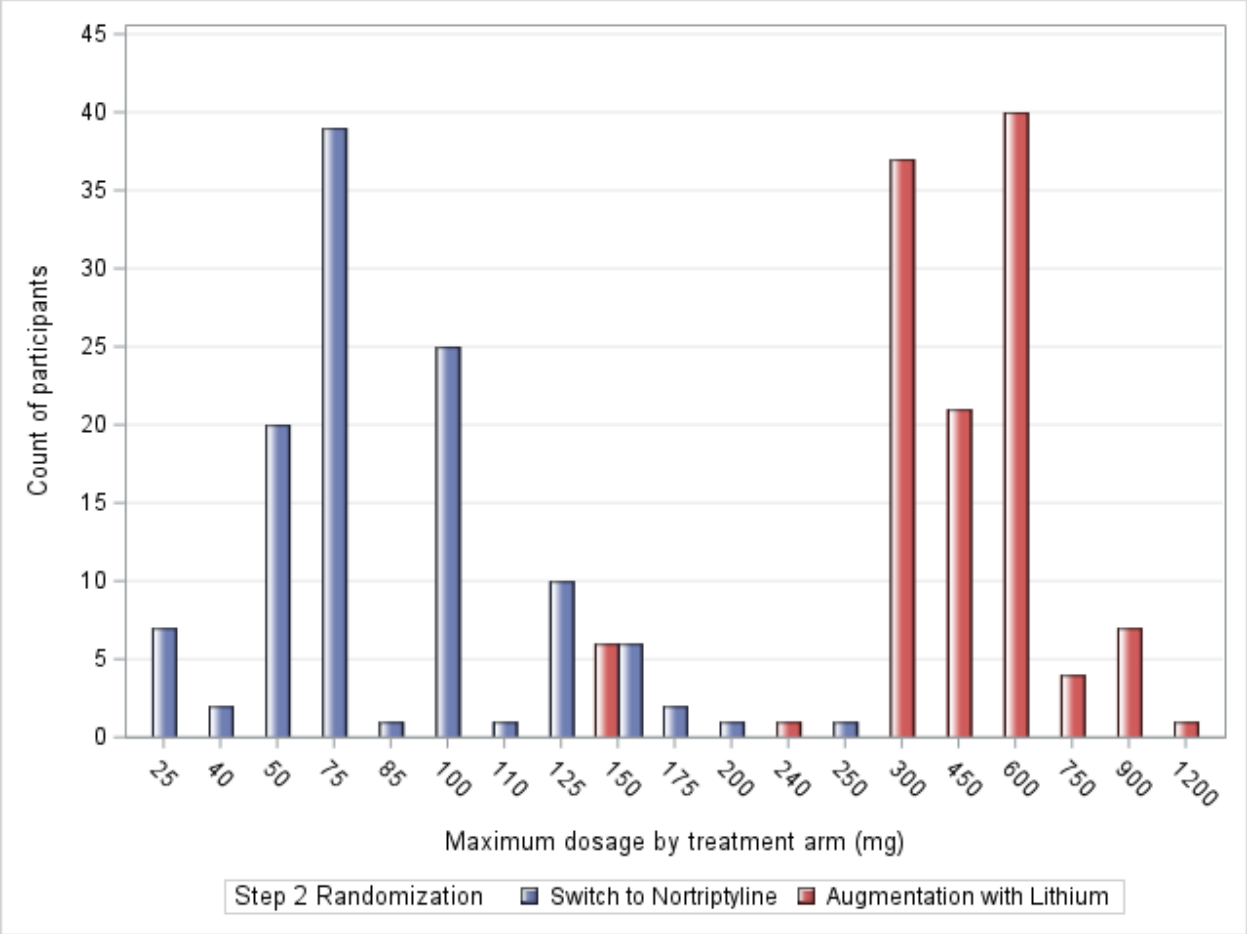
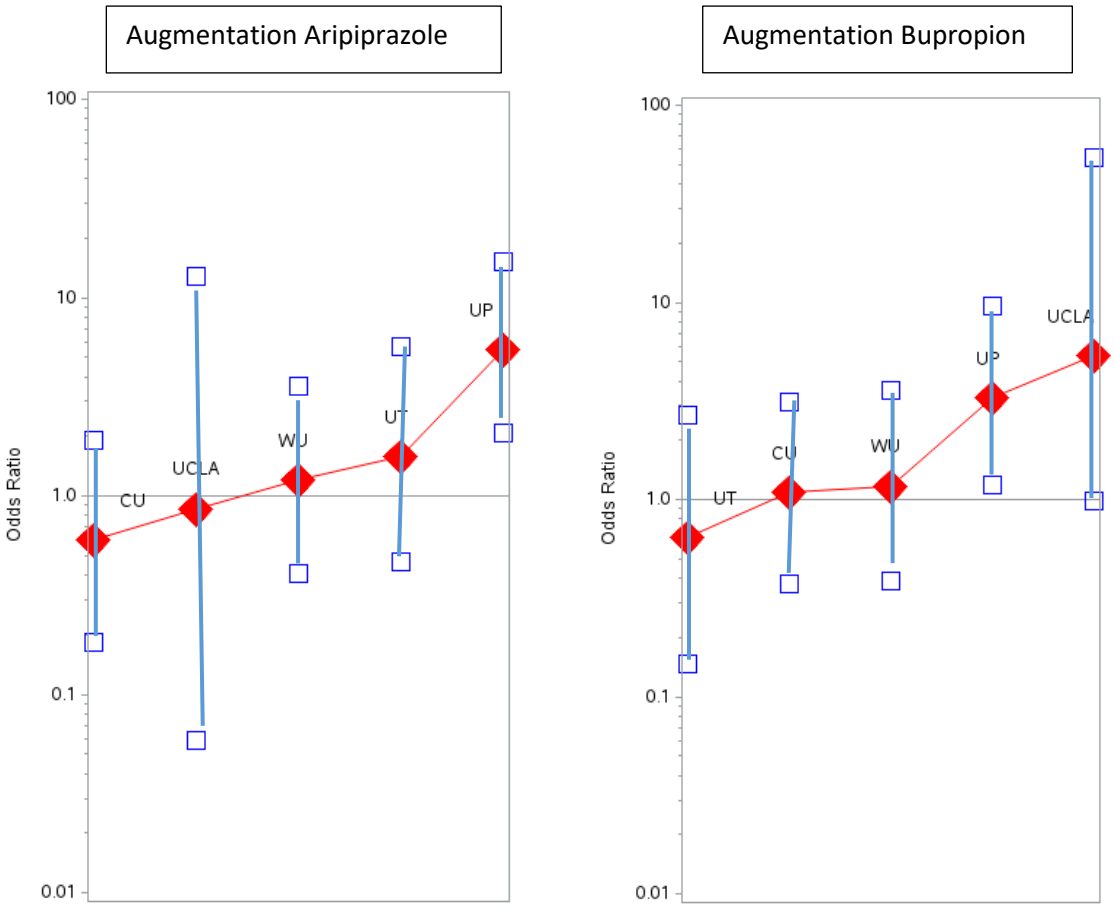


Figure S5: Caterpillar Plot of Step 1 Augmentation Arms vs Switch Arm

The caterpillar plots below show the odds ratios for remission of each of the Step 1 augmentation arms against the bupropion switch treatment arm for remission, based upon the 5 trial sites. Simple odds ratios are displayed by a red diamond, along with exact 95% confidence intervals as calculated by SAS PROC FREQ.



Abbreviations: CU, Columbia University; UCLA, University of California, Los Angeles; WU, Washington University; UT, University of Toronto; UP, University of Pittsburgh

Table S1. Representativeness of the Study Participants
Per *NEJM* requirements, Table S1 provides information concerning late-life depression in older adults with regard to socio-demographic characteristics. It summarizes the representativeness of participants.

Category	
Disease, problem, or condition under investigation	Late-Life Depression (LLD)[1]
Special considerations related to	
Sex and gender	Older women suffer from depression at twice the rate of older men. (ratio 2:1)
Age	LLD is diagnosed in older adults ≥60 years
Race or ethnic group	Depression is underdiagnosed and undertreated among Black Americans and Latinos. Somatization of psychological distress has been observed in Korean and Chinese older adults. Amongst Chinese-American older adults, the notion that depression brings dishonor and shame to one's family was believed to deter help seeking.
Socioeconomic status (SES)	Patients with LLD and lower SES have higher rates of morbidity and mortality compared with patients with LLD and higher SES. Additionally, patients with low SES tend to respond poorly to antidepressant treatment.
Other considerations	Patients with LLD often do not perceive a need for mental health care services. Stigma frequently prevents acknowledgement of depressive symptoms and interferes with proper medication adherence. Stigma is also considered to be a fundamental reason why older-adults do not seek treatment and discontinue treatment within primary care settings.
Overall representativeness of this trial	This pragmatic trial exemplified real-world treatment. The participants in the present trial demonstrated an expected ratio of women to men (around 2:1). Options for gender were male and female. The number of participants belonging to traditionally underrepresented racial or ethnic minority group was representative of real-world demographics. In regard to race, participants were asked, "What race do you identify as?" Options were Black/African American, White, Hawaiian/Pacific Islander, Asian, American Indian/Alaska Native/First Nations, Multi-race, and Other. The proportion of Black patients who underwent randomization was small overall (6.7%), but is consistent with lifetime prevalence rates in older African Americans (5.8%)[2]. Ethnicity was also reported by participants; they were asked, "Do you identify as Hispanic/Latino or Non-Hispanic?" The proportion of Hispanic patients was 7.4% which was also low. Possible explanations include the prevalence of stigma surrounding mental health disorders as well as disparities of access to mental health treatment.

References to Inform Table S1:

1. Hall CA, Reynolds-Iii CF. Late-life depression in the primary care setting: challenges, collaborative care, and prevention. Maturitas. 2014 Oct;79(2):147-52. doi: 10.1016/j.maturitas.2014.05.026. Epub 2014 Jun 7. PMID: 24996484; PMCID: PMC4169311.

2. Pickett YR, Bazelais KN, Bruce ML. Late-life depression in older African Americans: a comprehensive review of epidemiological and clinical data. Int J Geriatr Psychiatry. 2013 Sep;28(9):903-13. doi: 10.1002/gps.3908. Epub 2012 Dec 7. PMID: 23225736; PMCID: PMC3674152.

Index Medications

The table below summarizes the different index medications participants were taking in each treatment arm. In some circumstances, participants were taking two index medications, in addition to their trial medication.

Table S2. Index Medications Taken by Step 1 and Step 2 Participants

	Step 1			Step 2	
	Augment-Aripiprazole (N=211)	**Augment-Bupropion (N=206)**	**Switch-Bupropion (N=202)**	**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Index Antidepressant –no.					
Amitriptyline	0	0	1	0	0
Bupropion	6	1	10	37	44
Citalopram	17	20	22	8	6
Desvenlafaxine	8	3	1	1	3
Duloxetine	46	44	46	30	19
Escitalopram	36	38	33	16	12
Fluoxetine	21	18	19	7	2
Levomilnacipran	1	1	0	0	0
Mirtazapine	8	10	14	4	7
Moclobemide	0	1	0	0	0
Paroxetine	7	6	5	2	3
Sertraline	23	25	21	6	13
Trazodone	0	0	2	0	0
Venlafaxine	34	34	27	16	19
Vilazodone	0	2	1	1	0
Vortioxetine	2	1	5	2	3

In Step 1, 9 patients were taking more than 1 index medication. In Step 2, 15 patients were taking more than 1 index medication.

Psychological Well-Being

Psychological well-being was assessed using the NIH Toolbox Psychological Well-Being subscales of Positive Affect and General Life Satisfaction, with a T-score calculated as the average of these two subscales. The table below includes the least square mean T-scores and 95% confidence intervals for each of the subscales. Data regarding the Psychological Well-Being least square mean T-scores is included in the Results section of the primary manuscript (Table 2).

Table S3: Psychological Well-Being Subscale T-Scores

	Step 1				**Step 2**	
	Augment-Aripiprazole (N=211)	**Augment-Bupropion (N=206)**	**Switch-Bupropion (N=202)**		**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Outcome						
General Life Satisfaction[1] – least Square Mean T-score (95% CI)						
Baseline	35.28 (33.99 to 36.57)	36.19 (34.88 to 37.50)	35.05 (33.73 to 36.37)		33.46 (31.71 to 35.20)	34.00 (32.21 to 35.78)
Week 10	39.78 (38.43 to 41.12)	39.94 (38.57 to 41.32)	36.94 (35.49 to 38.38)		36.31 (34.42 to 38.21)	36.55 (34.64 to 38.45)
Change	4.50 (2.64 to 6.36)	3.75 (1.86 to 5.65)	1.88 (-0.03 to 3.80)		2.86 (0.41 to 5.30)	2.55 (0.07 to 5.03)
Positive Affect[1] – least Square mean T-score (95% CI)						
Baseline	31.37 (30.22 to 32.51)	31.17 (30.02 to 32.33)	31.38 (30.23 to 32.53)		29.79 (28.26 to 31.33)	30.85 (29.27 to 32.42)
Week 10	36.54 (35.34 to 37.73)	36.09 (34.89 to 37.29)	33.58 (32.31 to 34.85)		33.28 (31.61 to 34.94)	32.65 (30.97 to 34.33)
Change	5.17 (3.56 to 6.77)	4.92 (3.28 to 6.55)	2.20 (0.51 to 3.89)		3.48 (1.33 to 5.64)	1.80 (-0.38 to 3.99)

[1] Analyzed with mixed model, repeated measures ANOVA. Values are least square means and 95% confidence Intervals. T-score metric: population mean=50.

Mean Changes in Step 1 and Step 2 Outcomes Using Observed Data

The table below compares the observed mean change scores (plus standard deviations) for the primary and secondary outcome measures, to the best estimates of changes (these estimates also shown in Table 2 of the primary manuscript). As can be seen in the side-by-side comparison below, the actual values for the raw mean change scores from baseline to Week 10 align with the best estimates of change. For example, based upon the observed mean change scores, among the 183 patients in the augment-aripiprazole treatment arm who had a MADRS score at baseline and week 10, the average reduction was -7.82 points (SD: 8.15), in the 175 patients in the augment-bupropion arm, -6.68 points (SD: 7.35), and in the 163 patients in the switch-bupropion arm, -3.95 points (SD: 8.80). Based upon the best estimates of change (least square mean, 95% CI), reductions from baseline in MADRS scores were -7.60 (95% CI, -9.20 to -5.99), -7.23 (95% CI, -8.86 to -5.59), and -4.14 (95% CI, -5.81 to -2.48) points, for augment-aripiprazole, augment-bupropion, and switch-bupropion, respectively.

Table S4a. Comparison of Step 1 Observed Score Mean Change vs Least Square Mean Change Best Estimates

	Step 1 Observed Score Mean Change			**Step 1 Best Estimates of Change**		
	Augment-Aripiprazole **Mean Change (SD)**	**Augment-Bupropion** **Mean Change (SD)**	**Switch-Bupropion** **Mean Change (SD)**	**Augment-Aripiprazole** **Least Square Mean Change (95% CI)**	**Augment-Bupropion** **Least Square Mean Change (95% CI)**	**Switch-Bupropion** **Least Square Mean Change (95% CI)**
Outcome Measures						
Psychological Well-Being	4.79 (7.72)	4.10 (6.53)	1.80 (8.02)	4.83 (3.28 to 6.38)	4.33 (2.76 to 5.91)	2.04 (0.43 to 3.66)
MADRS	-7.82 (8.15)	-6.68 (7.35)	-3.95 (8.80)	-7.60 (-9.20 to -5.99)	-7.23 (-8.86 to -5.59)	-4.14 (-5.81 to -2.48)
Social Participation	2.78 (7.95)	2.51 (6.96)	1.36 (7.18)	3.09 (1.51 to 4.68)	2.46 (0.86 to 4.06)	1.95 (0.29 to 3.60)
Physical Function	-0.43 (4.89)	0.28 (5.09)	-0.03 (5.37)	-0.03 (-1.64 to 1.57)	0.53 (-1.10 to 2.15)	-0.33 (-2.06 to 1.40)

Table S4b. Comparison of Step 2 Observed Score Mean Change vs Least Square Mean Change Best Estimates

	Step 2 Observed Score Mean Change		Step 2 Best Estimates of Change	
	Augment-Lithium **Mean Change (SD)**	**Switch-Nortriptyline** **Mean Change (SD)**	**Augment-Lithium** **Least Square Mean Change (95% CI)**	**Switch-Nortriptyline** **Least Square Mean Change (95% CI)**
Outcome Measures				
MADRS	-4.11 (8.89)	-4.88 (9.34)	-4.63 (-6.78 to -2.49)	-5.33 (-7.52 to -3.14)
Psychological Well-Being	2.42 (8.26)	2.37 (7.28)	3.17 (1.12 to 5.22)	2.18 (0.10 to 4.26)
Social Participation	0.81 (7.96)	1.04 (8.69)	1.46 (-0.53 to 3.44)	1.57 (-0.45 to 3.58)
Physical Function	1.26 (4.68)	0.45 (5.86)	1.50 (-0.56 to 3.56)	1.00 (-1.09 to 3.09)

Sensitivity Analysis Comparing Remission Findings Based Upon Pre-Specified Definition vs Multiple Imputation

Based upon the pre-specified definition of remission, when both a MADRS and a PHQ-9 at week 10 were unavailable because the step was discontinued prematurely, the remission status was defined as 'non-remitter.' A sensitivity analysis applying multiple imputation was conducted. This multiple imputation approach used variables from both visits, as well as baseline variables from Table 1. Remission was defined as an imputed MADRS score ≤10 when an observed score was unavailable. As shown below, in Step 1, when applying multiple imputation, the percentage of participants who remitted are higher, but the risk ratios are lower. This is because the dropout rate in switch-bupropion was higher than the other treatment groups. For example, 39 participants (19.3%) were missing a Week 10 MADRS in the bupropion-switch group compared to 28 participants (13.3%) in the augment-aripiprazole group. In the primary analysis, based upon the pre-specified definition of remission, participants who discontinued the step prematurely were coded as non-remitters. However, in the sensitivity analysis using multiple imputation, these participants were coded as 'remitters.'

Table S5a: Comparison of Step 1 Remission Using Pre-Specified Definition vs Multiple Imputation

	Step 1 Remission Using Pre-Specified Definition			**Step 1 Remission Using Multiple Imputation**		
	Augment-Aripiprazole **N=211**	**Augment-Bupropion** **N=206**	**Switch-Bupropion** **N=202**	**Augment-Aripiprazole** **N=211**	**Augment-Bupropion** **N=206**	**Switch-Bupropion** **N=212**
Outcome						
Remission[1]--% (no.), Risk Ratio compared to bupropion switch (95% CI)	28.9% (61) 1.50 (1.06 to 2.13)	28.2% (58) 1.49 (1.04 to 2.12)	19.3% (39) 1.00 (reference)	30.6% (64.5)[2] 1.28 (0.88 to 1.87)	31.1% (64.1)[2] 1.32 (0.87 to 1.93)	24.1% (48.6)[2] 1.00 (reference)

[1] The number of participants missing a Week 10 MADRS were 28, 31, and 39 in the augment-aripiprazole, augment-bupropion, and switch-bupropion switch groups, respectively. [2] Average number over the 50 multiple imputations

Table S5b: Comparison of Step 2 Remission Using Pre-Specified Definition vs Multiple Imputation

	Step 2 Remission Using Pre-Specified Definition		**Step 2 Remission Using Multiple Imputation[1]**	
	Augment-Lithium (N=127)	**Switch-Nortriptyline (N=121)**	**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Outcome				
Remission--% (no.), Risk Ratio compared to nortriptyline switch (95% CI)	18.9% (24) 0.84 (0.53 to 1.36)	21.5% (26) 1.00 (reference)	22.9% (29.1) 0.85 (0.55 to 1.32)	26.8% (32.5) 1.00 (reference)

[1] The number of participants missing a Week 10 MADRS were 11 and 13 in the lithium augmentation and nortriptyline switch groups, respectively. [2] Average number over the 50 multiple imputations.

Sensitivity Analysis Excluding Patients Previously Exposed to a Step 1 Study Medication
Some participants reported exposure to a Step 1 study medication prior to enrolling in the trial (i.e., was previously prescribed aripiprazole or bupropion). A sensitivity analysis was conducted examining remission rates and change in MADRS scores, excluding participants who had any prior trial (including an inadequate trial) to a Step 1 treatment. The sample size for this sensitivity analysis was 485 (augment-aripiprazole, N=165; augment-bupropion, N=167; switch-bupropion, N=153). This analysis was only completed for Step 1, as Step 2 participants rarely reported prior exposure to lithium or nortriptyline. The same analytical techniques described in Methods for analysis of remission and change in depression were used for this sensitivity analysis.

Shown below is a side-by-side comparison of the sensitivity (subset) analysis and the main full group analysis. Findings are comparable: although the augmentation vs. switch analysis of remission was not statistically significant, the size of the difference was essentially the same as for the total group.

Table S6. Step 1 Sensitivity Analysis Excluding Patients Previously on a Step 1 Medication

Table S6a. Remission Outcome

Randomization Group	**Total ITT Group**		**Sensitivity Subset**	
	Remission	%	Remission	%
Augment-Aripiprazole	61/211	28.9	51/165	30.9
Augment-Bupropion	58/206	28.2	47/167	28.1
Switch-Bupropion	39/202	19.3	34/153	22.2

Table S6b. Secondary Outcome: MADRS Scores

Randomization Group	**Total ITT group**		**Sensitivity Subset**	
	Baseline[1]	Change[1]	Baseline[1]	Change[1]
Augment-Aripiprazole	23.4 (22.3 to 24.6)	-7.6 (-9.3 to -6.0)	23.5 (22.2 to 24.8)	-8.5 (-10.4 to -6.6)
Augment-Bupropion	22.9 (21.7 to 24.0)	-7.3 (-9.0 to -5.7)	23.2 (21.9 to 24.5)	-7.6 (-9.5 to -5.7)
Switch-Bupropion	22.6 (21.4 to 23.7)	-4.0 (-5.7 to -2.3)	22.6 (21.2 to 23.9)	-4.2 (-6.2 to -2.3)

[1] Values are least squares means and confidence intervals. Multiple imputation was not used as reported in primary manuscript.

Adherence Sensitivity Analysis

As this was a pragmatic study, all levels of adherence were allowed; therefore, individuals randomized to a study arm (e.g., augment-aripiprazole) could have stopped the treatment early or received another treatment instead, per their preference or their provider's preference. Adherent was defined as reaching a target dosage of the assigned treatment strategy and staying on that randomized treatment strategy throughout acute treatment. A total of 371 of the 619 Step 1 participants were adherent (augment-aripiprazole, N=150; augment-bupropion, N=134; switch-bupropion, N=87). A total of 128 of the 248 Step 2 participants were adherent (augment-lithium, N=58; augment-nortriptyline, N=70). An adherence sensitivity analysis was conducted, excluding participants who were not adherent. Table S5 summarizes adherence characteristics and reasons for non-adherence.

Table S7: Adherence Sensitivity Analysis

Table S7a. Treatment Outcome Combining Adherence and Remission Rates

	Step 1				**Step 2**	
	Augment-Aripiprazole (N=211)	**Augment-Bupropion (N=206)**	**Switch-Bupropion (N=202)**		**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Adherence Characteristic						
Adherent --% (no.)						
Stayed on randomized treatment at target dosage	71.1% (150/211)	65.0% (134/206)	43.1% (87/202)		45.7% (58/127)	57.9% (70/121)
Adherent who remitted	33.3% (50/150)	29.9% (40/134)	23.0% (20/87)		20.7% (12/58)	28.6% (20/70)
Both adherent and remitted	23.7% (50/211)	19.4% (40/206)	9.9% (20/202)		9.4% (12/127)	16.5% (20/121)
Non-adherent reasons --% (no.)						
Never started the randomized treatment	8.5% (18)	4.9% (10)	8.9% (18)		7.1% (9)	5.8% (7)
Discontinued the randomized treatment	10.4% (22)	10.7% (22)	24.3% (49)		35.4% (45)	22.3% (27)
Stayed on the randomized treatment, but below target dosage	8.5% (18)	15.5% (32)	12.9% (26)		11.0% (14)	9.9% (12)
Continued randomized treatment but added another antidepressant[1]	0.5% (1)	1.9% (4)	9.9% (20)		0.8% (1)	3.3% (4)
Lost to follow-up or unable to get data	0.9% (2)	1.9% (4)	1.0% (2)		0.0% (0%)	0.8% (1)

Note: "non-adherent" indicated that the patient, their clinician, and/or the study investigators at that site utilized a different treatment strategy than the randomization assignment.

[1] In the case of the switch assignments (bupropion switch or nortriptyline switch) this was typically restarting the index antidepressant that had been discontinued to implement the switch.

Sensitivity Analysis Comparing Full ITT Sample to Adherent Subsample

The tables below show side-by-side comparison of the full ITT sample vs. the adherent sub-sample for remission and change in Montgomery-Asberg Depression Rating Scale (MADRS) scores. The conclusion is that the findings are essentially unchanged, albeit with higher remission rates and greater MADRS change in the adherent sample with most study arms. In other words, the superiority of aripiprazole and bupropion augmentation vs. bupropion switch is not simply due to lower rates of adherence in the switch arm.

Table S7b. Adherence Sensitivity Analysis for Acute Step 1 and Step 2

Randomization Group	**Total ITT Group**		**Adherent Subset**	
	Remission	%	Remission	%
Step 1: Augment-Aripiprazole	61/211	28.9	50/150	33.3
Step 1: Augment-Bupropion	58/206	28.2	40/134	29.9
Step 1: Switch-Bupropion	39/202	19.3	20/87	23.0
Step 2: Augment-Lithium	24/127	18.9	12/58	20.7
Step 2: Switch-Nortriptyline	26/121	21.5	20/70	28.6

Falls During Acute Phase

To translate into clinically understandable terms, we report fall data as rates in the primary manuscript (See Results, Table 3). This table provides detailed information regarding the way falls were assessed, percent of no falls vs percent of any falls during acute treatment, as well as injurious falls and fall rates.

Table S8. Proportion of Biweekly Fall Assessments That Endorsed a Fall During Acute Step 1 and Step 2

	Step 1				Step 2	
	Augment-Aripiprazole (N=211)	**Augment-Bupropion (N=206)**	**Switch-Bupropion (N=202)**		**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Falls[1]						
Total Number of Fall Assessments	936	888	854		558	535
No Falls -- % (no.)	93.9% (879)	91.0% (808)	92.6% (791)		93.2% (520)	93.8% (502)
Any Falls -- % (no.)	6.1% (57)	9.0% (80)	7.4% (63)		6.8% (38)	6.2% (33)
1 fall -- % (no.)	5.1% (48)	6.4% (57)	6.0% (51)		4.3% (24)	4.3% (23)
2 falls -- % (no.)	0.5% (5)	1.4% (12)	1.2% (10)		1.1% (6)	1.3% (7)
3 (or more) falls -- % (no.)	0.4% (4)	1.2% (11)	0.2% (2)		1.4% (8)	0.6% (3)
Injurious Fall[2] -- % (no.)	3.8% (36)	5.9% (52)	4.5% (38)		4.8% (27)	3.0% (16)
Total Number of Falls[3]	70	114	77		60	46
Fall Rate[4]	0.33	0.55	0.38		0.47	0.38

[1] Falls were assessed during each bi-weekly study call or visit. We report the total number of fall assessments in this table. The denominators used to calculate percent of no falls vs any falls were based on the total number of fall assessments conducted during the ten-week treatment period.

[2] Participants were asked if they experienced an injurious fall. These totals represent the number of participant responses that endorsed injurious fall.

[3] Total number of falls was calculated by multiplying the number of participants who experienced 1, 2, and 3 or more falls (3 was used for calculation purposes). For example, in augmentation with aripiprazole, 48 participants X 1 fall + 5 participants X 2 falls + 4 participants X 3 falls (48 + 10 + 12=70).

[4] Fall rate was calculated based upon total number of falls divided by total number of participants in acute treatment arm phase (e.g., in augmentation with aripiprazole, 70 falls/211 participants=0.33).

Table S9: Serious Adverse Events (SAEs) in Acute Step 1 and Step 2

	Step 1				Step 2	
	Augment-Aripiprazole (N=211)	**Augment-Bupropion (N=206)**	**Switch-Bupropion (N=202)**		**Augment-Lithium (N=127)**	**Switch-Nortriptyline (N=121)**
Total SAEs (no.)	**15**	**16**	**24**		**13**	**11**
Relatedness to Intervention						
Probably or Possibly Related (no.)	**1**	**7**	**3**		**5**	**4**
	Hospitalized for pneumonia	Hospitalized for fall-related injury and sepsis due to pyelonephritis/UTI	Hospitalized for high blood pressure		Hospitalized for mental status changes	Psychiatric hospitalization (Diagnosis unknown)
		Hospitalized for fall	Hospitalized for high blood pressure		Hospitalized for fall-related injury and pulmonary embolism	Hospitalized for dizziness and shortness of breath
		Hospitalized for fall**	Hospitalized for delirium		Hospitalized for fall and acute renal insufficiency	Hospitalized for cardiac symptoms
		Hospitalized for increased frequency of falls			Hospitalized for acute exacerbation of COPD and pneumonia.	Fall-related injury*
		Psychiatric hospitalization (psychotic depression)			Hospitalized for dehydration and AKI	
		Psychiatric hospitalization (Involuntary)				
		Hospitalized for fall-related injury				

Not Likely Related (no.)	**14**	**9**	**21**		**8**	**7**
	Hospitalized for fall-related injury	Fall (required surgery)	Prostate cancer/surgery		Hospitalized for ischemic stroke	Hospitalized for nausea, vomiting, and diarrhea
	Death of unknown cause*, **	Hospitalized for pneumonia	Hospitalized for back pain		Hospitalized for a-fib	Hospitalized for CVA
	Hospitalized for lymphoma	Hospitalized for dehydration and weakness	Fall related-injury (required surgery)		Hospitalized for PE and blood clots in leg	Hospitalized for nausea, vomiting, chest pain
	Hospitalized for fall-related injury (required surgery)*	Hospitalized for colon surgery for diverticulosis and cholelithiasis	Hospitalized for lower back and leg pain*		Hospitalized for abdominal pain	Psychiatric hospitalization (diagnosis unknown)
	Hospitalized for tachycardia, dehydration, weakness*	Hospitalized for hypokalemia and dysarthria*	Hospitalized for viral illness*		Hospitalized for surgery for infected knee replacement	Hospitalized for surgery for pre-existing condition
	Hospitalized for non-cardiac chest pain	Hospitalized for retroperitoneal hematoma	Hospitalized for shoulder pain		Hospitalized for pneumonia	Hospitalized for a-fib w/RVR
	Hospitalized for chest pain (unknown cause)	Psychiatric Hospitalization (Diagnosis unknown, ECT)	Hospitalized for chills and weakness		Hospitalized for vertebral surgery	Hospitalized for colitis
	Hospitalized for fall-related injury	Hospitalized for TIA	Hospitalized for bleeding from abscess cavity		Hospitalized for blood clots	
	Hospitalized for shortness of breath	Hospitalized for shortness of breath	Hospitalized for heart failure*			
	Hospitalized for dyspnea		Hospitalized for hospital-			

			acquired pneumonia			
	Hospitalized for severe anemia		Hospitalized for nose bleed			
	Hospitalized for unspecified neurological event		Hospitalized for pneumonia			
	Hospitalized for electrolyte imbalance		Hospitalized for strangulated hernia (treated with surgery)			
	Hospitalized for fall-related injury (required surgery)		Hospitalized for pneumonia**			
			Hospitalized for general decline			
			Hospitalized for shortness of breath after elective surgery			
			Hospitalized for diarrhea and weakness			
			Hospitalized for fall-related injury			
			Hospitalized for fall-related injury			
			Hospitalized for fall			

			Hospitalized for intestinal inflammation			

In Step 1, a total of 55 SAEs were experienced in 49 participants. In the switch to bupropion group, 3 participants experienced 2 SAEs and 1 participant experienced 3 SAEs. In Step 2, a total of 24 SAEs were experienced in 22 participants. In the augmentation with lithium arm, 1 participant experienced 2 SAEs; in the switch to nortriptyline arm, 1 participant experienced 2 SAEs.

*Randomized and had not yet or never started treatment at time of SAE.

**Resulted in death.

Table S10. Adverse Events in Acute Step 1 and Step 2 (total 2288 AEs across all patients/all study arms/both Steps)

	Augment-Aripiprazole (N=211)	Augment-Bupropion (N=206)	Switch-Bupropion (N=202)	Augment-Lithium (N=127)	Switch-Nortriptyline (N=121)	Total for All Treatment Arms	Percent Based on Total AEs Across All Patients and Study Arms[1]
Total AEs in Arm	596	453	515	347	377	2288	
Total AEs per patient	2.82	2.20	2.55	2.73	3.12	2.64	
Accommodation Disturbances/Blurred Vision*							
Total	7	7	5	1	3	23	1.01
Mild	5	6	3	0	3		
Moderate	1	1	0	0	0		
Severe	0	0	2	0	0		
Akathesia							
Total	23	2	5	2	0	32	1.40
Mild	12	2	3	1	0		
Moderate	10	0	2	1	0		
Severe	1	0	0	0	0		
Asthenia/Lassitude/Increased Fatiguability*							
Total	18	11	3	18	11	61	2.67
Mild	10	4	1	6	5		
Moderate	6	5	2	10	5		
Severe	2	1	0	2	1		
Chest Pain*							
Total	4	0	1	1	3	9	0.39
Mild	1	0	0	0	1		
Moderate	3	0	1	1	0		
Severe	0	0	0	0	0		
Cold/flu symptoms*							
Total	29	18	23	13	13	96	4.20

Mild	14	8	8	5	8		
Moderate	14	10	10	4	5		
Severe	1	0	5	2	0		
Concentration Difficulties							
Total	11	4	10	9	10	44	1.92
Mild	4	3	5	5	4		
Moderate	5	1	5	4	4		
Severe	2	0	0	0	2		
Constipation*							
Total	15	20	18	6	20	79	3.45
Mild	10	14	11	4	9		
Moderate	5	5	3	1	9		
Severe	0	0	4	1	2		
Decreased Appetite W/O Weight Loss*							
Total	6	5	7	5	5	28	1.22
Mild	5	4	5	2	3		
Moderate	1	0	2	1	1		
Severe	0	0	0	2	1		
Diarrhea							
Total	14	13	11	8	7	53	2.32
Mild	8	10	6	4	4		
Moderate	4	2	4	4	3		
Severe	2	1	1	0	0		
Diminished Sexual Desire							
Total	1	0	0	0	3	4	0.17
Mild	0	0	0	0	2		
Moderate	1	0	0	0	0		
Severe	0	0	0	0	1		
Dizziness/Impaired Balance*							
Total	36	41	40	28	21	166	7.26
Mild	20	24	11	13	15		

Moderate	13	14	24	14	5		
Severe	3	1	4	1	1		
Dystonia							
Total	0	1	0	1	0	2	0.09
Mild	0	1	0	1	0		
Moderate	0	0	0	0	0		
Severe	0	0	0	0	0		
Elevated Blood Sugar							
Total	2	0	0	1	3	6	0.26
Mild	2	0	0	0	2		
Moderate	0	0	0	1	1		
Severe	0	0	0	0	0		
Emotional Indifference							
Total	1	0	0	1	1	3	0.13
Mild	1	0	0	0	0		
Moderate	0	0	0	0	0		
Severe	0	0	0	1	1		
Erectile Dysfunction							
Total	0	0	1	0	0	1	0.04
Mild	0	0	0	0	0		
Moderate	0	0	1	0	0		
Severe	0	0	0	0	0		
Extremity Swelling*							
Total	7	2	0	4	5	18	0.79
Mild	5	1	0	2	3		
Moderate	2	1	0	0	1		
Severe	0	0	0	0	1		
Failing Memory (independent of concentration difficulties)							
Total	7	6	3	6	4	26	1.14

Mild	6	4	1	2	1		
Moderate	1	2	2	2	3		
Severe	0	0	0	2	0		
Fall*							
Total	11	16	15	10	5	57	2.49
Mild	5	6	2	3	1		
Moderate	5	9	11	5	2		
Severe	1	1	2	0	2		
GI Distress							
Total	27	35	37	20	20	139	6.08
Mild	13	19	17	6	8		
Moderate	11	11	11	9	10		
Severe	3	5	9	5	2		
Headache							
Total	16	17	15	13	6	67	2.93
Mild	10	9	5	3	3		
Moderate	5	5	7	9	3		
Severe	1	3	3	1	0		
Hyperkinesia							
Total	0	2	1	1	0	4	0.17
Mild	0	1	0	0	0		
Moderate	0	1	1	1	0		
Severe	0	0	0	0	0		
Hypokinesia/Akinesia							
Total	1	1	0	0	1	3	0.13
Mild	0	0	0	0	1		
Moderate	0	1	0	0	0		
Severe	1	0	0	0	0		
Hypertension							
Total	3	1	3	1	1	9	0.39
Mild	3	0	2	1	1		

Moderate	0	1	1	0	0		
Severe	0	0	0	0	0		
Increased Appetite Without Weight Gain							
Total	23	2	6	2	6	39	1.70
Mild	15	2	4	2	5		
Moderate	8	0	1	0	1		
Severe	0	0	1	0	0		
Increased Dream Activity							
Total	7	5	8	1	5	26	1.14
Mild	3	3	5	1	4		
Moderate	4	1	3	0	1		
Severe	0	1	0	0	0		
Increased Duration of Sleep							
Total	2	2	2	0	2	8	0.35
Mild	1	1	1	0	2		
Moderate	0	1	1	0	0		
Severe	1	0	0	0	0		
Increased Salivation							
Total	1	0	1	0	0	2	0.09
Mild	1	0	0	0	0		
Moderate	0	0	1	0	0		
Severe	0	0	0	0	0		
Increased Sexual Desire							
Total	0	1	0	1	0	2	0.09
Mild	0	1	0	0	0		
Moderate	0	0	0	1	0		
Severe	0	0	0	0	0		
Increased Tendency to Sweat*							
Total	5	8	5	3	6	27	1.18
Mild	1	4	3	1	2		

Moderate	3	2	1	2	3		
Severe	1	1	1	0	1		
Irritability or Emotional Lability							
Total	10	12	34	5	15	76	3.32
Mild	6	8	17	3	9		
Moderate	4	4	13	2	6		
Severe	0	0	4	0	0		
Micturition Disturbances							
Total	3	2	2	2	4	13	0.57
Mild	2	2	1	2	3		
Moderate	1	0	0	0	1		
Severe	0	0	1	0	0		
Musculoskeletal Pain*							
Total	14	11	17	6	15	63	2.75
Mild	6	3	6	2	6		
Moderate	7	7	9	4	5		
Severe	1	1	2	0	3		
Orgasmic Dysfunction							
Total	1	2	0	0	0	3	0.13
Mild	0	2	0	0	0		
Moderate	1	0	0	0	0		
Severe	0	0	0	0	0		
Outpatient Surgery							
Total	8	10	9	4	5	36	1.57
Mild	0	0	0	0	0		
Moderate	8	9	8	3	4		
Severe	0	1	1	1	1		
Palpitations/Tachycardia							
Total	2	3	4	1	3	13	0.57
Mild	2	2	2	1	2		

Moderate	0	0	1	0	1		
Severe	0	1	1	0	0		
Paresthesia							
Total	0	0	2	1	1	4	0.17
Mild	0	0	0	0	1		
Moderate	0	0	2	1	0		
Severe	0	0	0	0	0		
Polyuria/Polydipsia*							
Total	5	0	6	11	1	23	1.01
Mild	2	0	3	6	0		
Moderate	0	0	2	2	0		
Severe	3	0	1	3	0		
Pruritus							
Total	3	5	1	5	1	15	0.66
Mild	0	4	0	3	1		
Moderate	1	1	1	1	0		
Severe	2	0	0	1	0		
Rash							
Total	3	8	4	3	1	19	0.83
Mild	2	5	3	1	1		
Moderate	1	3	1	1	0		
Severe	0	0	0	1	0		
Reduced or Disturbed Sleep*							
Total	39	18	33	6	6	102	4.46
Mild	20	9	14	3	2		
Moderate	11	5	10	1	3		
Severe	8	3	9	2	1		
Reduced Salivation (Dryness of Mouth)*							
Total	15	30	23	13	51	132	5.77
Mild	8	15	11	7	16		

Moderate	5	12	9	4	24		
Severe	1	2	3	0	11		
Rigidity							
Total	1	0	1	1	1	4	0.17
Mild	0	0	1	0	0		
Moderate	0	0	0	1	1		
Severe	1	0	0	0	0		
Shakiness							
Total	1	2	0	1	0	4	0.17
Mild	1	2	0	0	0		
Moderate	0	0	0	1	0		
Severe	0	0	0	0	0		
Shortness of Breath							
Total	7	1	3	3	1	15	0.66
Mild	5	0	1	1	1		
Moderate	2	1	2	2	0		
Severe	0	0	0	0	0		
Sleepiness/Sedation*							
Total	20	9	3	11	12	55	2.40
Mild	14	8	2	8	8		
Moderate	5	0	1	3	4		
Severe	1	0	0	0	0		
Slurred Speech							
Total	1	1	1	1	0	4	0.17
Mild	1	0	1	1	0		
Moderate	0	1	0	0	0		
Severe	0	0	0	0	0		
Tension/Inner Unrest/Anxiety							
Total	30	20	29	8	9	96	4.20
Mild	15	9	8	2	3		

Moderate	11	9	13	6	3		
Severe	4	2	8	0	3		
Tinnitus							
Total	0	3	7	2	0	12	0.52
Mild	0	2	5	1	0		
Moderate	0	1	0	1	0		
Severe	0	0	2	0	0		
Tremor*							
Total	14	20	13	34	4	85	3.72
Mild	13	11	4	15	2		
Moderate	1	7	8	15	2		
Severe	0	1	1	4	0		
Urinary Incontinence							
Total	3	0	1	2	0	6	0.26
Mild	0	0	1	1	0		
Moderate	2	0	0	0	0		
Severe	1	0	0	1	0		
Urinary Tract Infection							
Total	5	1	0	1	3	10	0.44
Mild	2	1	0	1	2		
Moderate	3	0	0	0	1		
Severe	0	0	0	0	0		
Vertigo							
Total	0	1	3	0	0	4	0.17
Mild	0	0	2	0	0		
Moderate	0	1	1	0	0		
Severe	0	0	0	0	0		
Weight Gain							
Total	32	3	1	8	4	48	2.10
Mild	17	1	1	4	2		

Moderate	11	2	0	2	1		
Severe	4	0	0	2	1		
Weight Loss (Baseline=0)							
Total	3	2	4	2	1	12	0.52
Mild	0	2	1	1	1		
Moderate	2	0	3	1	0		
Severe	1	0	0	0	0		
Other*							
Total	99	68	95	60	78	400	17.48
Mild	56	26	39	31	39		
Moderate	32	29	39	20	22		
Severe	11	9	11	5	11		

[1] A total of 2288 AEs occurred across all trial patients in both Steps. This number was calculated by taking the total number of AEs in the different categories (e.g., akathesia, chest pain, etc.), then dividing by total AEs across all patients in all study arms. For example, there were 32 reports of akathisia. To calculate percentage: 32 reports of akathisia in all treatment steps/2288 total AEs X 100=1.40%. The AE categories with the 5 highest percentages are reported in Table 3 in the primary manuscript.

*Severity level missing for some adverse events in this category.

References for Appendix

1. Hall CA, Reynolds-Iii CF. Late-life depression in the primary care setting: challenges, collaborative care, and prevention. Maturitas. 2014 Oct;79(2):147-52. doi: 10.1016/j.maturitas.2014.05.026. Epub 2014 Jun 7. PMID: 24996484; PMCID: PMC4169311.

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