Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial

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Summary

Background Treatment-resistant major depression is common and potentially life-threatening in elderly people, in whom little is known about the benefits and risks of augmentation pharmacotherapy. We aimed to assess whether aripiprazole is associated with a higher probability of remission than is placebo.

Methods We did a randomised, double-blind, placebo-controlled trial at three centres in the USA and Canada to test the efficacy and safety of aripiprazole augmentation for adults aged older than 60 years with treatment-resistant depression (Montgomery Asberg Depression Rating Scale [MADRS] score of ≥15). Patients who did not achieve remission during a pre-trial with venlafaxine extended-release (150–300 mg/day) were randomly assigned (1:1) to the addition of aripiprazole (target dose 10 mg [maximum 15 mg] daily) daily or placebo for 12 weeks. The computer-generated randomisation was done in blocks and stratified by site. Only the database administrator and research pharmacists had knowledge of treatment assignment. The primary endpoint was remission, defined as an MADRS score of 10 or less (and at least 2 points below the score at the start of the randomised phase) at both of the final two consecutive visits, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00892047.

Findings From July 20, 2009, to Dec 30, 2013, we recruited 468 eligible participants, 181 (39%) of whom did not remit and were randomly assigned to aripiprazole (n=91) or placebo (n=90). A greater proportion of participants in the aripiprazole group achieved remission than did those in the placebo group (40 [44%] *vs* 26 [29%] participants; odds ratio [OR] 2·0 [95% CI 1·1–3·7], p=0·03; number needed to treat [NNT] 6·6 [95% CI 3·5–81·8]). Akathisia was the most common adverse effect of aripiprazole (reported in 24 [26%] of 91 participants on aripiprazole *vs* one [1%] of 90 on placebo). Compared with placebo, aripiprazole was also associated with more Parkinsonism (15 [17%] of 86 *vs* two [2%] of 81 participants), but not with treatment-emergent suicidal ideation (13 [21%] of 61 *vs* 19 [29%] of 65 participants) or other measured safety variables.

Interpretation In adults aged 60 years or older who do not achieve remission from depression with a first-line antidepressant, the addition of aripiprazole is effective in achieving and sustaining remission. Tolerability concerns include the potential for akathisia and Parkinsonism.

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Introduction

Major depressive disorder is common in adults aged 60 years and older, leading to disability, suicidality, and increased mortality, but can be mitigated by treatment.[1,2] Most older adults with depression receive treatment in general medical settings, and the geriatric mental health workforce projections show that most older adults with depression will continue to be treated chiefly in the primary care sector.[3] A major problem is treatment resistance to first-line therapies: 55–81% of older adults with major depressive disorder fail to remit with a selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI).[4–6] Yet, unlike adults aged younger than 60 years,[7] little evidence exists from controlled trials to guide second-line or augmentation pharmacotherapy.[8,9] Second-line treatments including mirtazapine, bupropion, and augmentation with lithium, psychostimulants, or second-generation antipsychotics, interpersonal psychotherapy, and electroconvulsive therapy, have been proposed. Of these treatments, replicated evidence in older adults support only lithium augmentation, which is often difficult to tolerate in this age group.[8–10] Without evidence, clinicians cannot weigh the benefits and risks of these treatments in older adults.[11]

Research in context

Evidence before this study

We searched PubMed and ClinicalTrials.gov for studies published or underway up until December 2014 that examined augmentation or second-line pharmacotherapy for treatment-resistant depression in older adults with the following search terms: "treatment resistance", "depression", "elderly", "augmentation strategy", "aripiprazole", and "antidepressant". The search also used our familiarity with the medical literature and research in progress in the specialty.

As described in two critical reviews of the topic, few trials of any kind and no well powered trials exist to provide evidence for clinicians to make well reasoned decisions about second-line treatment in the common scenario of treatment-resistant late-life depression.

Added value of this study

Our findings bridge a crucial gap by providing clinicians with evidence on the benefits and risks of augmenting antidepressant treatment with an atypical antipsychotic, aripiprazole, in older adults with depression that did not remit with a serotonin–norepinephrine reuptake inhibitor.

Implications of all of the available evidence

About half of older adults with a major depressive disorder do not remit with first-line antidepressant pharmacotherapy. Aripiprazole has a favourable risk–benefit ratio in these older adults, most of whom receive treatment in primary care or general medical settings. The number needed to treat (NNT) with aripiprazole of 6·6 (95% CI 3·5–81·8) is similar to the NNT in young adults of the two most well studied augmentation therapies: lithium (NNT=5) and atypical antipsychotics (NNT=9).

Aripiprazole is a second generation (atypical) antipsychotic drug approved by the US Food and Drug Administration for augmentation treatment of major depressive disorder. Its pharmacodynamic actions include dopamine D2 and D3 receptor partial agonism and serotonin 5-HT_{1a} and 5-HT_{2a} receptor antagonism.[12,13] Results of industry-sponsored trials in younger depressed adults, generally aged 18–65 years (average age in their 30s), have shown the efficacy of aripiprazole as an augmentation to SSRIs or SNRIs.[14]However, few data exist to clarify benefits of aripiprazole in older adults with major depressive disorder.[15–17] Additionally, little is known about its safety and tolerability in this age group. This absence of information is worrying because treatment with aripiprazole in younger patients with major depressive disorder is associated with neurological and cardiometabolic adverse effects, particularly akathisia (restlessness) and weight gain.[14] Older adults might be more susceptible to such adverse effects.[11] Lastly, antipsychotics are associated with increased mortality in older adults with dementia, possibly owing to QTc prolongation, arrhythmias, and sudden cardiac death.[11]

For the **protocol** see healthymind.wustl.edu/trd/aripiprazole

Aripiprazole augmentation has potential benefits and risks in the treatment of late-life depression, neither of which is adequately informed by existing data. Accordingly, we did a trial of aripiprazole augmentation in adults aged 60 years or older whose depression did not respond to an adequate trial of venlafaxine. We postulated that aripiprazole would be associated with a higher probability of remission, a greater improvement of depressive symptoms and resolution of suicidal ideation, and a greater stability of remission than placebo. We also hypothesised that use of aripiprazole might lead to an increased risk of akathisia. Finally, we also examined treatment-emergent Parkinsonism, tardive dyskinesia, and change in adiposity, weight, lipids, glucose, and QTc.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled trial of aripiprazole augmentation in adults aged 60 years or older whose depression did not respond to an adequate trial of venlafaxine in three academic centres (University of Pittsburgh, PA, USA [coordinating site]; Centre for Addiction and Mental Health, Toronto, ON, Canada; and Washington University, St Louis, MO, USA) after approval by the institutional review boards. An independent data and safety monitoring board oversaw the study. The protocol is available online.

We started open treatment with venlafaxine extended release in 468 participants to establish, prospectively, treatment resistance, defined by failure to remit after at least 12 weeks of treatment with at least 4 weeks at the highest tolerated dose (minimum of 150 mg/day and maximum 300 mg/day). Remission was defined as a Montgomery Asberg Depression Rating Scale (MADRS) score of 10 or less at both of the final two consecutive visits. Most participants were treated for 12–14 weeks but protocol guidelines allowed for a longer trial (up to 24 weeks) if needed to clarify remission status.

From July 20, 2009, to December 30, 2013, we recruited adults aged 60 years and older, who met the Diagnostic and Statistical Manual of Mental Disorders criteria for major depressive episode with at least moderate symptoms, as defined by a Montgomery Asberg Depression Rating Scale[18] score of 15 or more (range 0–60; higher scores show increased severity of depression). Exclusion criteria included dementia, bipolar disorder, schizophrenia, present psychotic symptoms, and alcohol or substance misuse or dependence within the past 6 months. Diagnosis of dementia was based on medical records, cognitive screening, a formal review of dementia criteria, and, for

unclear cases, an informant's interview. All participants provided written, informed consent.

Randomisation and masking

Participants who did not achieve remission with venlafaxine monotherapy were randomly assigned (1:1) to the addition of aripiprazole or placebo while maintaining the final dose of venlafaxine achieved during initial open treatment. Randomisation lists were created in Pittsburgh and distributed to the research pharmacists. The pharmacists randomised participants and emailed the data manager the assignments to enter and track in the database. The data manager and the pharmacists did not have any interaction with the participants or other involvement with study procedures. Randomisation was done using a permuted block approach to ensure treatment balance within each study site. Treatment was double-blind (masking was achieved with tablets of identical appearance); only the database administrator and research pharmacists had knowledge of treatment assignment.

Procedures

In the 12-week randomised phase, aripiprazole or matched placebo tablets were started at 2 mg daily and titrated as tolerated to a target dose of 10 mg daily that could be increased up to 15 mg daily if needed. To assess stability of remission, participants who achieved remission were then followed-up for an additional 12 weeks during which the study drug (aripiprazole or placebo) was continued under double-blind conditions. Adherence was monitored in all phases by self-report and pill counts. Follow-up visits occurred every 1–2 weeks in the first two phases of the study and every 2–4 weeks in the continuation phase. Visits consisted of assessments of depressive symptoms, suicidal ideation, and medication side effects, and routine management of any participant concerns.

Outcomes

The primary efficacy outcome was remission, defined as completion of the randomised phase with a MADRS score of 10 or less at both of the final two consecutive visits with at least a 2-point drop from the start of the phase. At these visits, the MADRS was measured by an independent assessor. To identify participants who needed a different intervention during the 12-week continuation phase, we ascertained relapse, defined as having enough symptoms to meet criteria for a present major depressive episode.[19] We also examined changes in the Hamilton Depression Rating Scale 17-item (Ham-D)[20] and both the resolution and the emergence of suicidal ideation using the Scale of Suicidal Ideation.[21] Finally, we examined changes in health-related quality of life, using the 36-item Medical Outcome Survey.[22]

Cardiometabolic indices were measured at the beginning and end of the randomised phase. The primary cardiometabolic outcome was change in whole body adiposity, quantified with dual-energy x-ray absorptiometry (DEXA) scanning.[23] We also measured changes in weight, fasting plasma lipids (total cholesterol, LDL, HDL, and triglycerides), and fasting blood glucose and insulin. We also measured changes in QTc on electrocardiography at the beginning and end of the 12-week randomised phase.

Self-reported somatic symptoms were elicited at each visit with the UKU scale,[24] which characterises 46 common side-effects of psychotropic medications; a side-effect was regarded as present if there was a 2-point increase on the corresponding UKU item. Finally, we recorded serious adverse events that resulted in death, life-threatening problems, persistent or substantial disability or incapacity, admission to hospital (or

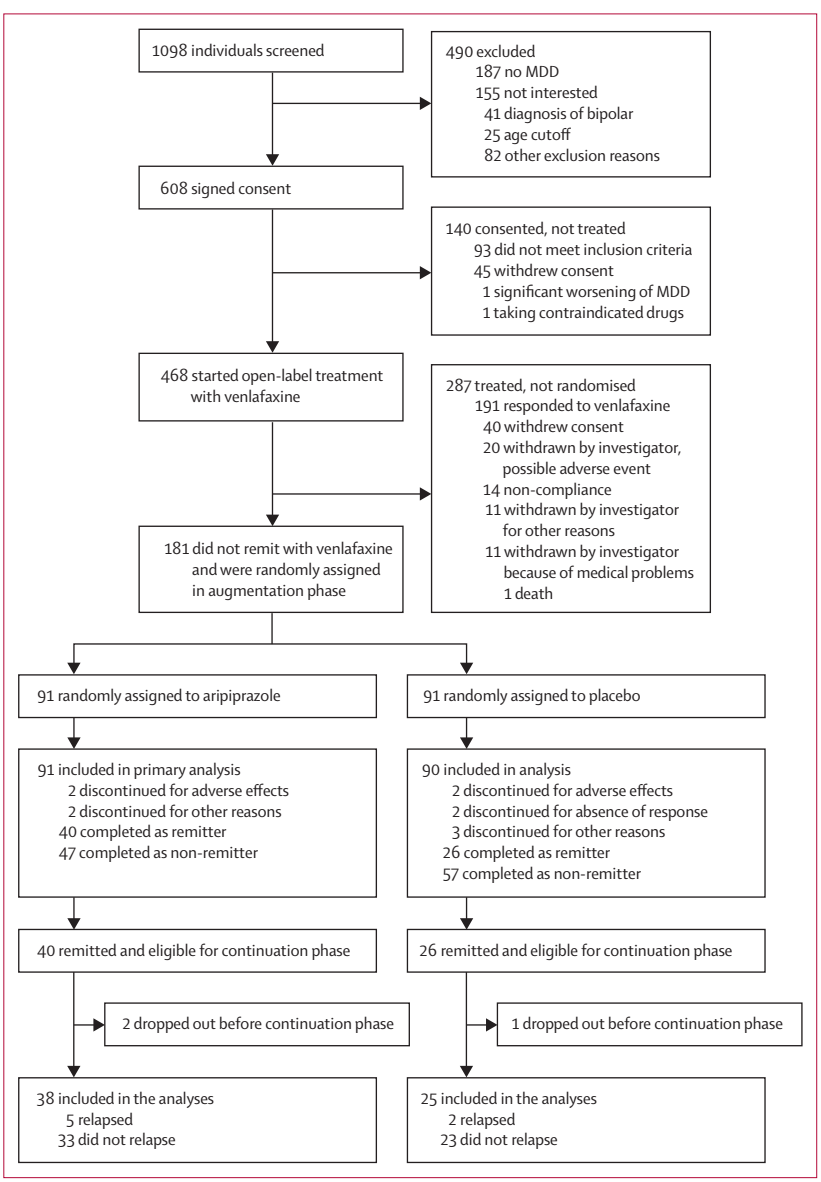

***Figure 1*: Trial profile**
MDD=major depressive disorder.

	Total (n=181)	Aripiprazole (n=91)	Placebo (n=90)
Age (years)	66·0 (62·8–70·5)	66·0 (62·8–70·5)	65·7 (62·8 –69·8)
>70 years	49 (27%)	27 (30%)	22 (24%)
Female participants	103 (57%)	52 (57%)	51 (57%)
White	159 (88%)	80 (88%)	79 (88%)
Education (years)	14·0 (12·0–16·0)	14·0 (12·0–16·0)	14·0 (12·0–16·0)
Cumulative Illness Rating Scale[28]			
Total score	9·0 (7·0–13·0)	10·0 (7·0–13·0)	9·0 (7·0–12·0)
Count	6·0 (4·0–7·0)	6·0 (4·0–8·0)	6·0 (4·0–7·0)
Diagnosed with diabetes	26 (15%)	16 (18%)	10 (11%)
Diagnosed with hypertension	94 (54%)	44 (51%)	50 (57%)
Number of co-prescribed non-study medications	5 (3–8)	5 (3–8)	6 (3–8)
Taking benzodiazepines	73 (40%)	36 (40%)	37 (41%)
RBANS Total Index Score*	95·0 (85·0–107·0)	98·0 (85·0–108·0)	94·0 (85·0–102·0)
Brief Symptom Inventory[29] Anxiety Subscale score†	0·8 (0·3–1·3)	1·0 (0·5–1·3)	0·5 (0·3–1·3)
Diagnosed with recurrent depression	129 (71%)	62 (68%)	67 (74%)
Age at first depressive episode (years)	40·0 (20·0–57·0)	44·0 (24·0–57·0)	35·0 (17·0–57·0)
Duration of present episode (weeks)‡	104·0 (35·0–364·0)	118·0 (45·0–364·0)	104·0 (28·0–317·0)
Did not respond to at least one adequate antidepressant trial during the present episode	132 (74%)	66 (73%)	66 (75%)
Montgomery-Asberg Depression Scale			
Enrolment	28·0 (25·0–32·0)	29·0 (25·0–33·0)	28·0 (24·0–32·0)
Randomisation	23·0 (18·0–28·0)	24·0 (18·0–29·0)	23·0 (18·0–26·0)
Venlafaxine dose at randomisation (mg/day)	300 (300–300)	300 (300–300)	300 (300–300)

Data are median (IQR) or n (%). RBANS=Repeatable Battery for the Assessment of Neuropsychological Status. *Data missing for 2 participants in the aripiprazole group and 1 in the placebo group. †Measured at randomisation (ie, end of initial open treatment with venlafaxine); scaled score mean is 100 and SD is 15.[30] ‡Data missing for 2 participants in the aripiprazole group.

Table 1: **Baseline demographic and clinical characteristics of participants randomly assigned to augmentation treatment with aripiprazole or placebo[28,31]**

prolongation of treatment in hospital), or medical or surgical intervention to prevent one of these outcomes.

Statistical analysis

Analyses were done with the intention-to-treat principle. We calculated that a sample size of 200 randomised participants would provide 80% power to show superior efficacy of aripiprazole, assuming a difference of 20% with placebo; we chose 20% as a credible and generally accepted threshold of meaningful clinical effect size. For the primary efficacy outcome, logistic regression compared the proportion of participants meeting criteria for remission at the end of the randomised phase; secondarily, we examined time to remission using a Cox model. For the secondary efficacy outcome of depressive symptom change we used mixed-effect modelling[25] examining non-linear trajectories and using the Bayesian information criterion to establish the best fitting model.[26] Following a strategy outlined by Senn,[27] we included site as a covariate in all efficacy analyses. For the primary neurological tolerability outcome, we examined the proportion of participants with akathisia (and, secondarily, the proportions with Parkinsonism and tardive dyskinesia). For the MADRS outcome measured longitudinally, we used mixed-effect models. For the primary cardiometabolic tolerability outcome, we measured change in DEXA total fat (and, secondarily, changes in body fat percentage, weight, lipids, glucose, and QTc) using mixed models. We used SAS (version 9) and R (version 3.0.1). We regarded p values of 0·05 or less were to be statistically significant. This trial is registered with ClinicalTrials.gov, number NCT00892047.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding and senior authors (EJL and CFR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 468 eligible participants recruited between July 20, 2009, and Dec 30, 2013, who started venlafaxine extended release, 96 (21%) did not complete the open treatment phase because they withdrew consent, were withdrawn by the investigator, or for other reasons; 191 (41%) participants remitted, 181 (39%) did not remit, 91 were randomised to aripiprazole, and 90 were randomised to placebo (figure 1, table 1).

40 (44%) of 91 participants randomly assigned to aripiprazole and 26 (29%) of 90 randomly assigned to placebo achieved remission, a significant difference

(table 2). Time to first remission similarly favoured aripiprazole (appendix). The median final aripiprazole dose was 7 mg per day (range 2–15) in remitters and 10 mg per day (range 2–15) in non-remitters (appendix). Participants assigned to aripiprazole had a larger decrease in their MADRS scores (figure 2) and Ham-D scores (appendix) than did those assigned to placebo. The MADRS was measured at each weekly or biweekly visit. We did regular intersite sessions to maintain inter-rater reliability (intraclass correlation coefficient [ICC] in this study was 0·997)

Extrapyramidal symptoms were measured at all visits by study physicians with three validated scales:29 the Barnes Akathisia Scale (outcome:global akathisia item), the Simpson Angus Scale (treatment-emergent Parkinsonism defined by a 2-point increase in total score), and the Abnormal Involuntary Movement Scale (global involuntary movements item). Inter-rater agreement for these scales was adequate to excellent (ICCs range 0·57–0·74) 30 (33%) of 91 participants assigned to aripiprazole and 25 (28%) of 90 assigned to placebo had suicidal ideation at baseline, which resolved in 22 (73%) of 30 participants in the aripiprazole group versus 11 (44%) of 25 in the placebo group (p=0·02).

The Medical Outcome Scale (MOS)-Physical Component Score changed from 42·9 (SD 12·8) to 40·9 (11·3) for participants in the aripiprazole group, and from 41·6 (11·4) to 41·4 (11·0) for participants in the placebo group (p=0·15). The participants assigned to aripiprazole had a greater improvement in the (MOS)-Mental Component Score than did placebo-treated participants (mean decrease 6·0; p=0·007).

One participant in the aripiprazole group died by suicide after 5 weeks of double-blind treatment; this act was neither due to emergent suicidal ideation nor to aripiprazole side-effects, but was concluded by investigators to be a result of the individual's persisting and longstanding suicidal ideation (table 3).

Five (5%) of 91 participants assigned to aripiprazole discontinued the study drug before the end of the randomised phase (one died by suicide, one discontinued because of jitteriness and akathisia, one discontinued because of worsening Parkinsonism, and two withdrew consent) versus eight (9%) of 90 participants assigned to placebo (two discontinued because of absence of efficacy, one discontinued because of worsening Parkinsonism, two discontinued because of headaches, and three withdrew consent). Serious adverse events were reported in four (5%) of 91 participants on aripiprazole (one died by suicide, one was admitted to hospital for congestive heart failure, one had a mild stroke, and one was admitted to hospital for diverticulitis) and two (2%) of 90 participants on placebo (one had a myocardial infarction and one was admitted to hospital for vomiting attributed to accidentally taking extra venlafaxine).

Of 46 possible side-effects queried, the most frequently reported with aripiprazole compared with placebo were increased dream activity (23 [27%] of 86 *vs* 12 [14%] of 87, weight gain 17 [20%] of 86 *vs* eight [9%] of 87), and tremor (five [6%] of 86 *vs* none of 87; appendix).

Akathisia was noted at some point during the randomised phase in more participants (n=13) assigned to aripiprazole than were assigned to placebo (p=0·02; table 3). Typically, akathisia was mild and did not persist to the end of the treatment phase; however, akathisia was associated with a temporary increase in suicidal ideation in three (3%) individuals in the aripiprazole group versus none in the placebo group. None of 85 patients in the aripiprazole group had dyskinesia versus two (2%) of 84 in the placebo group, whereas the

	Aripiprazole (n=91)	Placebo (n=90)	Odds ratio (95% CI)	p value
All patients	40 (44%)	26 (29%)	2·0 (1·1–3·7)	0·03
Site				0·047*
Toronto	7 (25%)	6 (24%)	1 (reference)	..
Pittsburgh	18 (60%)	8 (27%)	2·6 (1·2–5·8)	..
Washington	25 (45%)	12 (38%)	2·4 (1·1–5·3)	..

Interactions between cell and site variables are non-significant. Treatment and site at baseline used for calculation of odds ratio. *Test based on a Wald χ^2 statistic with 2 degrees of freedom.

Table 2: **Remission from depression during augmentation with aripiprazole or placebo**

See Online for appendix

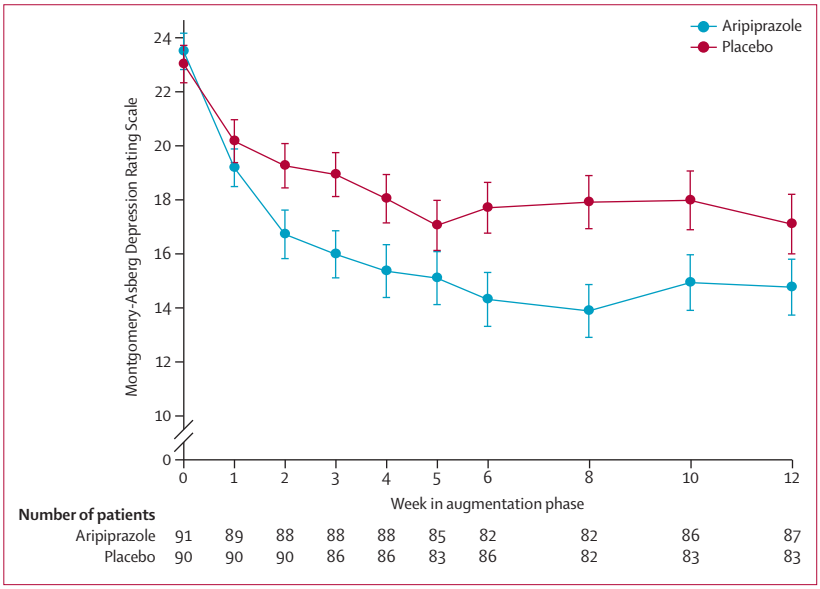

Figure 2: **Reduction in depressive symptoms during augmentation with aripiprazole or placebo**
Montgomery-Asberg Depression Rating Scale (MADRS) mean scores (bars show standard error of the mean so thatinference about the treatments can be visualised at each timepoint) plotted at the protocol-specified sampling times in the augmentation phase. Number of patients assessed at each time is shown at the bottom of the plot. Analyses used time as a continuous measure calculated using dates. Based on the Bayesian information criterion, a longitudinal mixed model with linear, quadratic, and cubic terms. The mixed model data shows that both groups improved over time but the aripiprazole group showed a significantly greater improvement and includes linear and quadratic differences (linear x cell F=9·7, p=0·0019; quadratic x cell F=6·8, p=0·009). Based on the modelled data, the aripiprazole group decreases 9·2 points over 12 weeks whereas the placebo group decreases roughly 5·9 points over the same time period.

	Aripiprazole (n=91)	Placebo (n=90)
SAEs	4 (4%)	2 (2%)
AEs leading to discontinuation of study medication	3 (3%)	3 (3%)
Emergent suicidal ideation (in those with no ideation at start of phase)	13/61 (21%)	19/65 (29%)
Suicide	1 (1%)	0
Extrapyramidal syndromes		
Akathisia	24 (26%)	11 (12%)
Mild	19 (21%)	9 (10%)
Moderate–severe	5 (5%)	2 (2%)
Persistent (still present at last visit of phase)	5/85 (6%)	2/84 (2%)
Dyskinesia	0/85	2/84 (2%)
Parkinsonism	15/86 (17%)	2/81 (2%)
QTc prolongation on electrocardiogram (to ≥480 ms)	1/78 (1%)	0/79
Mean QTc change (SD), ms	+1·9 (30·8)	+1·6 (25·9)

Data are n (%) or n/N (%), unless otherwise specified. AE=adverse event. SAE=severe adverse event.

Table 3: **Adverse events and tolerability measures during the augmentation phase**

proportion of patients with Parkinsonism was higher in the aripiprazole group than in the placebo group (table 3). Both akathisia and Parkinsonism occurred at a median aripiprazole dose of 7 mg per day (IQR 5–10; range 2–15).

Participants assigned to aripiprazole had a greater increase in bodyweight, but not in total body fat, than those assigned to placebo (figure 3). No differences were reported between groups in changes in percentage of body fat, or in total cholesterol, HDL, LDL, triglycerides, glucose, or insulin concentrations (appendix).

63 (95%) of 66 remitters (38 in the aripiprazole group and 25 in the placebo group) participated in the 12-week continuation phase. The two groups did not differ significantly with respect to proportion of patients with depression relapse or change in MADRS scores (appendix). The proportion of patients with dyskinesia in this phase was two (5%) of 38 for aripiprazole and one (4%) of 25 for placebo. Mean bodyweight changes in this phase were an increase of 0·84 kg (SD 2·55) in the aripiprazole group and a decrease of 0·16 kg (2·49) in the placebo group; we did not measure DEXA body fat or any other cardiometabolic biomarkers in this phase.

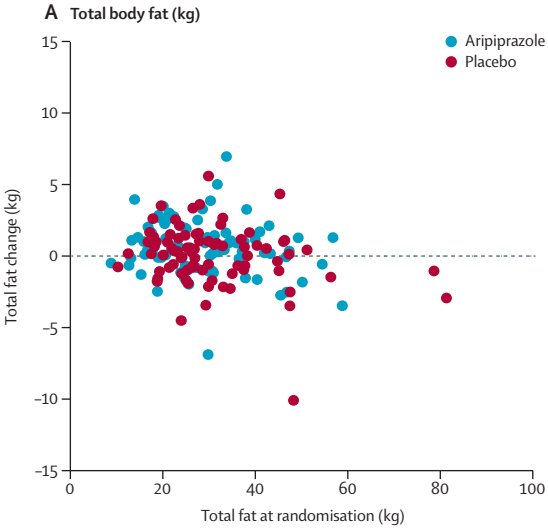

Figure 3: **Changes in cardiometabolic variables during augmentation with aripiprazole or placebo**

Mean total fat change (A) was +0·54 kg (SD 1·98) with aripiprazole (n=81) versus –0·06 (2·08) with placebo (n=83); p=0·064). Mean total weight change (B) was +1·93 kg (SD 3·00) with aripiprazole (n=84) versus +0·01 (3·15) with placebo (n=85); p<0·0001.

Discussion

This is the first randomised, double-blind, placebo-controlled trial of pharmacotherapy for treatment-resistant depression in late life. Our study had three main findings. First, the addition of aripiprazole was effective at getting older adults with treatment-resistant depression to remission and maintaining remission during 12 weeks of continuation. Second, aripiprazole was associated with some akathisia and Parkinsonism. Third, aripiprazole was not associated with an increase in cardiometabolic risk as measured by changes in whole body adiposity, plasma lipids, glucose, or insulin. These findings help clarify the risk–benefit ratio of aripiprazole augmentation for clinicians facing the common situation of treatment-resistant depression in their older patients.

Aripiprazole was effective in inducing remission, with a number needed to treat (NNT) of 6·6 (95% CI 3·5–81·8) relative to placebo, which is similar to augmentation treatments for treatment-resistant depression in young adults (lithium NNT=5 and atypical antipsychotics NNT=9).[14,32] For further perspective, an NNT of 13 for the overall efficacy of short-term pharmacotherapy of late-life depression has been reported.[33] Almost half (44%) of participants assigned to

aripiprazole remitted, despite their history of treatment resistance; none of the participants had remitted after moderate-to-high-dose SNRI treatment, and 75% had also not responded to at least one adequate antidepressant trial before enrolling in this study. By comparison, less than a third of younger patients (mean age of 41 years) with major depressive disorder and this extent of treatment resistance remit when given augmentation treatment in randomised trials.[7] The benefits of aripiprazole noted in our trial included a reduction of suicidal ideation. This finding is important because depressed older adults (many of whom have seen a primary care physician within the past month) are at high risk for death by suicide.[2] Moreover, the remission attained during the initial 12 weeks of treatment seemed stable over a 12-week continuation period. This interval is a short follow-up period, but most relapses in late-life depression occur soon after attaining remission.[19,34]

Our safety and tolerability data address several concerns about the use of atypical antipsychotics, particularly in older adults. First, the high proportion of young adults with depression who have akathisia while receiving aripiprazole[14] raises concerns because older adults might be at higher risk for extrapyramidal adverse effects than younger adults. Indeed, we reported a higher proportion of patients with akathisia in the aripiprazole group than in the placebo group. However, akathisia was typically mild, with similar proportions of patients affected in both groups by the end of the randomised phase, suggesting that it is transient and can be managed with watchful waiting or dose reduction. Akathisia was associated with a temporary increase in suicidal thoughts in three participants in the aripiprazole group, and it led to aripiprazole discontinuation in another one participant. These more concerning issues did not occur in any participant randomly assigned to placebo. Aripiprazole was also associated with a higher proportion of patients with Parkinsonism and complaints of tremor than was placebo. Clinicians need to be aware of these adverse effects of aripiprazole and adjust dose or potentially switch treatment. However, we noted no increased risk of tardive dyskinesia with aripiprazole relative to placebo during 24 weeks of treatment. This result is important because the incidence of tardive dyskinesia in patients aged 55 years and older has been reported to be as high as 25% during 6 months of exposure to first generation antipsychotics.[35] However, this present study does not address the question of risk of tardive dyskinesia with chronic (ie, ≥1 years) use of aripiprazole.

When assessing cardiometabolic risks, we did not find that aripiprazole significantly increased either the amount or percentage of body fat. Furthermore, aripiprazole did not cause an increase in fasting lipids, glucose, or insulin. Therefore, in the short term at least, aripiprazole did not typically induce cardiometabolic risks; of a mean average of 1·9 kg weight gain during 12 weeks of acute treatment, only about 30% was due to fat gain. Most weight gain might be either re-gain as described with successful antidepressant treatment,[36] hydration, or peripheral oedema as described with antipsychotic use.[11] The difference between the weight and adiposity changes underscores the importance of using direct measures of adiposity to characterise the effects of treatments on cardiometabolic risk.[37] Nevertheless, increases in adiposity, lipids, and glucose are well known adverse effects of atypical antipsychotics; clinicians need to follow guidelines and monitor cardiometabolic variables when prescribing aripiprazole.[38]

Additional safety concerns with antidepressant treatment include treatment-emergent suicidal ideation, which has been hotly debated since the advent of a so-called black box warning on all antidepressants for this risk in adolescents and young adults, but not in older adults.[39] We did not find any evidence for increased treatment-emergent suicidal ideation with aripiprazole. Nevertheless, we recommend continuing assessment of suicidal ideation and suicide risk in depressed older adults during treatment. Additionally, we did not detect any QTc prolongation with aripiprazole, which is important because many psychotropic medications have that potential, particularly in older adults.[29] Finally, drug interactions can occur between aripiprazole and some widely prescribed antidepressants (such as paroxetine and duloxetine), and we chose venlafaxine as a lead-in antidepressant in part to avoid this potential interaction.

Limitations of our study included the sample size being slightly smaller than our target sample size and including a small number of participants being aged 75 years and older, for whom cognitive impairment and incipient dementia is more likely than in younger patients. Also, with the exclusion of patients with dementia, our sample size, and the 12-week duration of follow-up, our study cannot fully address tolerability and safety concerns with aripiprazole in older adults, and it does not allay safety concerns with antipsychotic use in older adults with dementia.[11,40] In view of the high frequency of treatment non-response to first-line antidepressants, how aripiprazole augmentation should fit into structured depression management approaches for older adults is unclear.[41] For example, whether venlafaxine should be increased to very high doses (>300 mg per day) before attempting augmentation is unknown.

In conclusion, our results showed that aripiprazole is moderately effective in older adults with treatment-resistant depression. Clinicians prescribing this medication should be aware of its propensity to cause akathisia and Parkinsonism. However, the potential benefits of remission from depression and greater reductions in suicidal ideation outweigh these usually mild adverse events.

Contributors

EJL, BHM, JWN, MAD, MAB, and CFR designed the study and wrote the protocol. EJG, BHM, DMB, JFK, JAS, and CFR recruited patients for the study and participated in coordination. EJL, SJA, AEB, and CFR had access to all the data and analysed the data. EJL, BHM, SJA, and CFR were responsible for the decision to submit the report, and drafted it. All authors read, critically revised, and approved the report.

Declaration of interests

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