Incomplete Response in Late-life depression: Getting to REmission (IRL-GREY) study

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Disclosures

National Institute of Mental Health
National Institute on Aging
National Center for Minority Health and Health Disparities
National Heart, Lung, and Blood Institute
Centers for Medicare & Medicaid Services (CMS)
Patient Centered Outcomes Research Institute (PCORI)
John A. Hartford Foundation
American Foundation for Suicide Prevention
Commonwealth of Pennsylvania
Clinical and Translational Science Institute (CTSI)
National Palliative Care Research Center (NPCRC)
American Association for Geriatric Psychiatry (services as associate editor)
UPMC Endowment in Geriatric Psychiatry
Forest Laboratories, Pfizer, Lilly, BristolMyersSquibb
(provide pharmaceuticals for NIH-sponsored research)
Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized placebo-controlled trial.

Evidence before this study:

- Few trials of any kind and no well-powered trials currently 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 this critical gap by providing clinicians with evidence on the benefits and risks of augmenting an antidepressant with an atypical antipsychotic (aripiprazole) in older adults with a depression that did not remit with a serotonin-norepinephrine reuptake inhibitor
Research in Context

Implications of all available evidence:

• About one-half of older adults with a major depressive disorder do not remit with first-line antidepressant pharmacotherapy.
Research in Context

• Aripiprazole has a favorable risk/benefit ratio in these older adults, most of whom receive treatment in primary care or general medical settings.

  o The NNT of aripiprazole of 6.6 is comparable to the NNT in young adults of the two most well-studied augmentation therapies:
Research in Context

- Aripiprazole has a favorable risk/benefit ratio in these older adults, most of whom receive treatment in primary care or general medical settings.
  
  - The NNT of aripiprazole of 6.6 is comparable to the NNT in young adults of the two most well-studied augmentation therapies:
    
    - **lithium NNT= 5;**
    
    - **atypical antipsychotics NNT = 9;**
How common is treatment resistance in LLD?

- SSRI and SNRI monotherapy is well-defined first-step/second-step pharmacotherapy
- 55-81% of older adults will fail to remit
What are second-line options?

- Second line options include:
  - Mirtazapine
  - Bupropion
  - Li augmentation
  - Psychostimulants
  - SGAs
  - IPT
  - Neurostimulation (ECT, VNS, rTMS)

- Best evidence: Li augmentation
Rationale for IRL GREY Study

• Treatment resistance is very common in LLD
  - It is the rule, rather than the exception

• No clearly evidence-based options in this age group

• Risks and benefits may differ in older adults compared to young adults
  - Without evidence, clinicians cannot make informed choices for treatment
Aripiprazole augmentation for treatment-resistant depression

The IRL-GREY study design & efficacy results
IRL GREY: Study Design

**Phase 1 (N=468)**
12 week open-label
All subjects receive 6wk venla 150mg/d, then non-remitters receive 6wk venla 300mg/d

**Phase 2 (N=181)**
12 week acute augmentation
Randomization of phase1 venla non-remitters

**Phase 3 (N=63)**
12 week continuation
Remitters in phase 2 stay on blinded treatment

**Remission**: MADRS < 10 for at least two consecutive assessments

# Titration and Dosage

- **VENLA 300mg + PBO**
- **VENLA 300mg + ARIPIP**
- **VENLA 300mg + ARIPIP**

Aripip start 2.5mg: titrate weekly
Target dose: 10mg/d
Max dose: 15mg/d
Study flow

140 Consented, not treated:
- 93 Did not meet inclusion criteria
- 45 Withdrew Consent
- 1 Significant worsening of MDD
- 1 Taking contraindicated medication

490 Excluded:
- 187 No current MDD
- 155 Not interested
- 41 Diagnosis of Bipolar
- 25 Age cut-off
- 82 Other exclusion reasons

1098 Screened

608 Signed Consent

468 Started open-label treatment with venlafaxine ER

Non-remitter to venlafaxine ER and randomized into augmentation phase: 181

287 Treated, not randomized:
- 191 Responded to venlafaxine ER
- 40 Withdrew Consent
- 20 Withdrawn by PI, possible AE
- 14 Non-Compliance
- 11 Withdrawn by PI due to Other reasons
- 10 Withdrawn by PI due to medical problems
- 1 Death

91 Randomized to aripiprazole

90 Randomized to placebo

91 Included in analyses
- 2 discontinued for adverse effects
- 2 discontinued for other reasons
- 40 completed as remitter
- 47 completed as nonremitter

90 included in analyses
- 2 discontinued for adverse effects
- 2 discontinued for lack of response
- 3 discontinued for other reasons
- 26 completed as remitter
- 57 completed as nonremitter
# Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole (N=91)</th>
<th>Placebo (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>66.4 (62.8/71.6)</td>
<td>65.7 (62.8/69.8)</td>
</tr>
<tr>
<td>% (n) Female</td>
<td>57 (52)</td>
<td>57 (51)</td>
</tr>
<tr>
<td>% (n) White</td>
<td>88 (80)</td>
<td>88 (79)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>14.0 (12.0/16.0)</td>
<td>14.0 (12.0/16.0)</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale</td>
<td>10.0 (7.0/13.0)</td>
<td>9.0 (7.0/12.0)</td>
</tr>
<tr>
<td># of coprescribed medications</td>
<td>5 (3,8)</td>
<td>6 (3,8)</td>
</tr>
<tr>
<td>% taking benzodiazepines</td>
<td>40 (36)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>RBANS Total Index Score</td>
<td>98.0 (85.0/108.0)</td>
<td>94.0 (85.0/102.0)</td>
</tr>
<tr>
<td>% (n) with recurrent depression</td>
<td>68 (62)</td>
<td>74 (67)</td>
</tr>
<tr>
<td>Age at first depressive episode (yrs)</td>
<td>44.0 (24.0/57.0)</td>
<td>35.0 (17.0/57.0)</td>
</tr>
<tr>
<td>Duration of current episode (wks)</td>
<td>118.0 (45.0/364.0)</td>
<td>104.0 (28.0/317.0)</td>
</tr>
<tr>
<td>% (n) failed prior antidep trial</td>
<td>73 (66)</td>
<td>75 (66)</td>
</tr>
<tr>
<td>MADRS at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment</td>
<td>29.0 (25.0/33.0)</td>
<td>28.0 (24.0/32.0)</td>
</tr>
<tr>
<td>Randomization</td>
<td>24.0 (18.0/29.0)</td>
<td>23.0 (18.0/26.0)</td>
</tr>
<tr>
<td>Venlafaxine dose at randomization (mg/d)</td>
<td>300 (300/300)</td>
<td>300 (300/300)</td>
</tr>
</tbody>
</table>
Remission rate: 44% vs. 29%

- NNT = 6.6

- For perspective:
  - NNT 13 for acute pharmacotherapy in LLD
  - NNT 5 for Li augmentation in TRD
  - NNT 9 for atypical antipsychotics in TRD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>DF</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study arm</td>
<td>Aripiprazole vs. Placebo§</td>
<td>1</td>
<td>2.57</td>
<td>1.29 – 5.13</td>
<td>0.007</td>
</tr>
<tr>
<td>Site</td>
<td>Pittsburgh vs. Toronto§</td>
<td>2</td>
<td>1.76</td>
<td>0.74 – 4.20</td>
<td>0.30†</td>
</tr>
<tr>
<td></td>
<td>Washington University vs. Toronto§</td>
<td>2</td>
<td>1.93</td>
<td>0.80 – 4.66</td>
<td></td>
</tr>
<tr>
<td>Baseline MADRS</td>
<td>Continuous</td>
<td>1</td>
<td>0.92</td>
<td>0.87 – 0.98</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline anxiety score</td>
<td>Continuous</td>
<td>1</td>
<td>0.51</td>
<td>0.28 – 0.92</td>
<td>0.03</td>
</tr>
</tbody>
</table>

§ Indicates significance.
Improvement in depressive Sx

Montgomery Asberg Depression Rating Scale

Aripiprazole
Placebo
Aripiprazole effective dose

- Achieved remission at end of study (N=40)
- Did not achieve remission at end of study (N=51)
Reduction of suicidal ideation

• 30/91 (33.0%) participants on aripiprazole and 25/90 (27.8%) on placebo had suicidal ideation at baseline

• SI resolved in 22/30 (73.3%) aripiprazole vs. 11/25 (44.0%) placebo (p=0.02).
Study flow (continued)

40 Remitted and eligible for continuation phase

2 dropped out prior to continuation phase

38 Included in analyses
5 Relapsed
33 Did not relapse

26 Remitted and eligible for continuation phase

1 dropped out prior to continuation phase

25 Included in analyses
2 Relapsed
23 Did not relapse
Continued effectiveness in continuation Tx

Montgomery Asberg Depression Rating Scale

Aripiprazole
Placebo

Week in Continuation Phase

ARIP N = 38
PBO N = 25
Summary

• “Efficacious for TRLLD.”
  o Higher remission rate and more reduction of depressive symptoms, compared to placebo
  o Improvements generally maintained over 12 weeks of continuation
  o Reduction of suicidal ideation

• Further study?
  o Who benefits most?
  o Where does aripiprazole belong in a Tx algorithm?
Remission rates in aripiprazole vs. placebo stratified by the presence of set-shifting impairment
Remission rates in aripiprazole vs. placebo stratified by the presence of high anxiety
Aripiprazole augmentation for treatment-resistant depression

IRL-GREY safety and tolerability results
Extrapyramidal symptoms were measured at all visits by study physicians.

<table>
<thead>
<tr>
<th>Screen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes Akathisia Scale</td>
<td>global akathisia item</td>
</tr>
<tr>
<td>Simpson Angus Scale</td>
<td>treatment-emergent Parkinsonism defined by a 2-point increase in total score</td>
</tr>
<tr>
<td>Abnormal Involuntary Movement Scale</td>
<td>global involuntary movements item</td>
</tr>
</tbody>
</table>
Safety Outcomes

Cardiometabolic indices were measured at the beginning and end of the randomized phase.

The primary cardiometabolic outcome was change in whole body adiposity quantified using DEXA scanning.
Safety Outcomes

Cardiometabolic indices were measured at the beginning and end of the randomized phase.

Also measured changes in:

- Weight
- Fasting plasma lipids (total cholesterol, LDL, HDL, triglycerides)
- Fasting blood glucose and insulin
- QTc on EKG
Safety Outcomes

Recorded serious adverse events (SAEs) that resulted in death, life-threatening problems, persistent or significant disability or incapacity, hospitalization (or prolongation of hospitalization), or medical or surgical intervention to prevent one of these outcomes.
Tolerability Outcomes

• Self-reported somatic symptoms were elicited at each visit with the UKU scale which characterizes 46 common side effects of psychotropic medications

• A side effect was considered present if there was a 2-point increase on the corresponding UKU item
Extrapyramidal Symptoms (1)

• Akathisia was observed at some point during the randomized phase in 24/91 (26.7%) participants randomized to aripiprazole vs. 11/90 (12.2%) on placebo (exact p=0.02)

• This difference was primarily accounted for by mild (non-distressing) akathisia (19/91 [20.9%] on aripiprazole vs. 9/90 [10%] on placebo; exact p=0.16)
Extrapyramidal Symptoms (1)

- Akathisia was moderate or severe in 5 (5.5%) on aripiprazole vs. 2 (2.2%) on placebo (exact p=0.44)

- Akathisia was associated with a temporary increase in suicidal ideation in 3 (3.3%) on aripiprazole vs. 0 on placebo (exact p=0.26)
Extrapyramidal Symptoms (2)

- At the last visit, the rates of akathisia did not differ in the two groups (5/85 [5.9%] on aripiprazole vs. 2/84 [2.4%] on placebo; exact p=0.44)

- Similarly, the rates of dyskinesia did not differ (0/85 [0%] vs. 2/84 [2.4%], exact p=0.25) but the rate of Parkinsonism was higher with aripiprazole (15/86 [17.4%] than with placebo 2/81 [2.5%], exact p=0.001)
Extrapyramidal Symptoms (2)

- Both akathisia and Parkinsonism occurred at a median (Interquartile Range [IQR]) aripiprazole dose of 7mg (5, 10), range 2-15mg
Cardiometabolic outcomes

• Participants randomized to aripiprazole showed greater increase in body weight, but not in total body fat than those randomized to placebo.

• There were no differences between groups in changes in percentage of body fat, total cholesterol, HDL, LDL, triglycerides, glucose, or insulin levels.
Changes in Cardiometabolic Parameters during Augmentation with Aripiprazole or Placebo

Total body fat (in kg)

Mean (SD) total fat change was +0.54 kg (1.98) with aripiprazole (n=81) vs. -0.06 (2.08) with placebo (n=83), F(1,160)=3.49, P=0.064.

Weight (in kg)

Mean (SD) total weight change was +1.93 kg (3.00) with aripiprazole (n=84) vs. 0.01 (3.15) with placebo (n=85), F(1,165)=16.26, p<0.001.
# Changes in Cardiometabolic Parameters during Randomized Phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aripiprazole N=91 Mean (SD) change</th>
<th>Placebo N=90 Mean (SD) change</th>
<th>Testing Treatment controlling for site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>1.93 (3.00) [n=84]</td>
<td>0.01 (3.15) [n=85]</td>
<td>F(1,165)=16.26, p&lt;0.0001</td>
</tr>
<tr>
<td>DXA Total Body Fat (kg)</td>
<td>0.54 (1.98) [n=81]</td>
<td>-0.06 (2.08) [n=83]</td>
<td>F(1,160)=3.49, p=0.064</td>
</tr>
<tr>
<td>Total Fat (%)</td>
<td>0.15 (2.34) [n=81]</td>
<td>-0.03 (1.62) [n=83]</td>
<td>F(1,60)=0.32, p=0.57</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>4.84 (36.12) [n=80]</td>
<td>2.38 (35.30) [n=82]</td>
<td>F(1,158)=0.16, p=0.69</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>2.94 (7.86) [n=81]</td>
<td>1.66 (8.06) [n=81]</td>
<td>F(1,158)=1.01, p=0.32</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>0.71 (32.56) [n=81]</td>
<td>-3.55 (33.09) [n=79]</td>
<td>F(1,156)=0.62, p=0.43</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>1.37 (62.05) [n=80]</td>
<td>2.73 (53.34) [n=81]</td>
<td>F(1,157)=0.03, p=0.87</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>4.96 (25.54) [n=80]</td>
<td>4.56 (16.30) [n=84]</td>
<td>F(1,160)=0.01, p=0.91</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.27 (7.08) [n=78]</td>
<td>1.74 (7.48) [n=80]</td>
<td>F(1,143)=1.51, p=0.22</td>
</tr>
</tbody>
</table>

*All results represent change values (post-treatment minus pre-treatment).
Early discontinuation of medication and SAEs

- Aripiprazole discontinuation: 5/91 (5.5%) participants discontinued medication prior to the end of the randomized phase (1 completed suicide; 1 due to jitteriness/akathisia, 1 due to worsening Parkinsonism; and 2 withdrew consent)

exact $p=0.41$
Early discontinuation of medication and SAEs

- Placebo discontinuation: 8/90 (8.9%) participants discontinued medication (2 due to lack of efficacy; 1 due to worsening Parkinsonism; 2 due to headaches, and 3 withdrew consent)
Serious Adverse Events

• Aripiprazole SAE: Observed in 4/91 (5%), including completed suicide; hospitalized for congestive heart failure; suffered mild stroke; hospitalized for diverticulitis

• Placebo SAE: 2/90 (2%), including myocardial infarction; hospitalized for vomiting attributed to accidentally taking extra venlafaxine
Cardiac Safety

- No differences in mean (SD) change in QTc (aripiprazole: +1.9 sec (30.8); placebo: +1.6 (25.9); $F[1,155]=0.0$, $p=0.96$)

- No differences in the proportion of participants whose QTc increased from $<480$ to $>480$) (1/78 [1.3%] on aripiprazole vs. 0/79 on placebo, exact $p=0.50$)
Tolerability

• Out of 46 possible side effects queried, more participants on aripiprazole than on placebo experienced increased dream activity (26.7% vs. 13.8%), tremor (5.8% vs. 0%), and weight gain (19.8% vs. 9.2%)
Thanks to the National Institute for Mental Health for primary funding; thanks to Hartford Foundation, Taylor Family Institute, CFMRI, and NCATS for ancillary funding, and to Bristol-Myers Squibb and Pfizer for supplying medications.
The Joy of Old Age.
(No Kidding.)

I look forward to being 80... I begin to feel not a shrinking but an enlargement of mental life and perspective. One has had a long experience of life, not only one’s own life, but others’ too... One is more conscious of transience and perhaps of beauty. At 80 one can take a long view and have a vivid, lived sense of history not possible at an earlier age... I do not think of old age as an ever grimmer time that one must somehow endure and make the best of, but as a time of leisure and freedom, freed from the factitious urgencies of earlier days, free to explore whatever I wish, and to bind the thoughts and feelings of a lifetime together... I look forward to being 80.
“Those who allege that old age is devoid of useful activity...are like those who say that the pilot does nothing in the sailing of his ship, because, while others are climbing the masts, or running about the gangways, or working at the pumps, he sits quietly in the stern and simply holds the tiller. He may not be doing what younger members of the crew are doing, but what he does is better and much more important.”

“It is not by muscle, speed, or dexterity that great things are achieved, but by reflection, force of character, and judgment.”

“In these qualities old age is usually not poorer, but is even richer.”

--Cato Maior, De Senectute
Cicero, Loeb Classical Library, 1923