Incomplete Response in Late-life depression: Getting to Remission

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

LENZE EJ, MULHART AK, BRENDINGER DM, KAPLANT, NEUMANN JP, ANDERSON JS, DWYER ML, REYNOLDS DF, REYNOLDS CF III. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized placebo-controlled trial. *Lancet*, 2015, online. PMCID: PMC4666813

Research in Context

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


Research in Context

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
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

What are second-line options?

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

- Best evidence: Li augmentation

Meta-analyses comparing psychotherapy & medication for geriatric depression & anxiety

Meta-analysis of response rates on drug vs placebo in 10 trials with 13 contrasts

For depression, effective first-line treatments include:

- Behavioral activation
  - PST
  - CBT
  - With or without medications

For anxiety, first-line treatment is selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitor medication.
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

**Phase 1** (N=468)

- 12 week open-label
  - 65% (n=300) receive placebo
  - 35% (n=168) receive aripiprazole 300mg/d

**Phase 2** (N=145)

- 12 week acute augmentation
- Randomization of Phase 1 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

- **Aripiprazole start** 2.5mg: titrate weekly
- **Target dose** 10mg/d
- **Max dose** 15mg/d

**VENLA 300mg**

- **VENLA 300mg + ARIPIP**

- **VENLA 300mg**

**Comparison of Antipsychotic ADE**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Sedation</th>
<th>EPS</th>
<th>AC</th>
<th>OH</th>
<th>QT</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>0</td>
<td>0+</td>
<td>+</td>
<td>0+</td>
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<tr>
<td>Haloperidol</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Quetiapine</td>
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<td>0+</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Risperidone</td>
<td>++</td>
<td>+</td>
<td>0+</td>
<td>++</td>
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**Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole (N=63)</th>
<th>Placebo (N=66)</th>
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</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>66.9 (56.7/75.4)</td>
<td>65.7 (62.8/70.8)</td>
</tr>
<tr>
<td>1.0 BMI</td>
<td>57 (52)</td>
<td>57 (52)</td>
</tr>
<tr>
<td>2.0 BMI</td>
<td>50 (45)</td>
<td>58 (53)</td>
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<tr>
<td>3.0 BMI</td>
<td>45 (40)</td>
<td>49 (44)</td>
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<td>4.0 BMI or more</td>
<td>40 (36)</td>
<td>40 (36)</td>
</tr>
<tr>
<td>5.0 BMI or more</td>
<td>40 (36)</td>
<td>40 (36)</td>
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<tr>
<td>6.0 BMI or more</td>
<td>40 (36)</td>
<td>40 (36)</td>
</tr>
<tr>
<td>7.0 BMI or more</td>
<td>40 (36)</td>
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<tr>
<td>8.0 BMI or more</td>
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<tr>
<td>9.0 BMI or more</td>
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<tr>
<td>10.0 BMI or more</td>
<td>40 (36)</td>
<td>40 (36)</td>
</tr>
<tr>
<td>BMI 15 kg/m² or more</td>
<td>94.0 (65.0/132.3)</td>
<td>94.0 (65.0/132.3)</td>
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<tr>
<td>11.0 kg/m² or more</td>
<td>60 (44)</td>
<td>70 (53)</td>
</tr>
<tr>
<td>Age at first depressive episode (yrs)</td>
<td>24.8 (16.8/37.9)</td>
<td>26.8 (17.2/37.8)</td>
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<tr>
<td>Duration of current episode (wks)</td>
<td>118.8 (65.0/194.4)</td>
<td>105.0 (26.0/197.0)</td>
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<tr>
<td>1.0 Medication prior episode (yrs)</td>
<td>75 (88)</td>
<td>75 (88)</td>
</tr>
<tr>
<td>2.0 Medication prior episode (yrs)</td>
<td>75 (88)</td>
<td>75 (88)</td>
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<tr>
<td>3.0 Medication prior episode (yrs)</td>
<td>75 (88)</td>
<td>75 (88)</td>
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**Courtesy of Shuja Hassan MD, Jen Naples PharmD, Joe Hanlon PharmD**
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>Cell</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>Study site</td>
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<tr>
<td>Aripiprazole vs. Placebo</td>
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<td>2.57</td>
<td>1.29 – 5.13</td>
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<tr>
<td>Pittsburgh vs. Toronto</td>
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<td>1.76</td>
<td>0.74 – 4.20</td>
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<td>Washington University vs. Toronto</td>
<td>1.93</td>
<td>0.80 – 4.66</td>
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<tr>
<td>Baseline MADRS</td>
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</tr>
<tr>
<td>Continuous</td>
<td>1</td>
<td>0.92</td>
<td>0.87 – 0.98</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous</td>
<td>0</td>
<td>0.85</td>
<td>0.81 – 0.90</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Improvement in Depressive Symptoms

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).

Aripiprazole effective dose

Continued effectiveness in continuation Tx

Summary

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

- Further study?
  - Who benefits most?
  - Where does aripiprazole belong in a Tx algorithm?
Remission rates in aripiprazole vs. placebo stratified by the presence of set-shifting impairment

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 (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)

• 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)

• 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

![Graph showing changes in total body fat and weight with aripiprazole and placebo](chart)

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)

- 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%)

With Thanks

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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.