EDITORIAL

Aripiprazole Augmentation in Older Persons with Treatment-Resistant Depression

Gemma Lewis, Ph.D., and Glyn Lewis, Ph.D.

Approximately 30% of patients treated for depression do not have a response to selective serotonin-reuptake inhibitors (SSRIs).[1] The next step in treatment has generally been to augment existing medication with either an antidepressant from a different class or an antipsychotic medication. Both strategies can be effective, although the degree of benefit has depended to some extent on which drug is added.[2] In a two-step trial, the results of which are now published in the *Journal*,[3] Lenze and colleagues investigated augmentation with either bupropion (a dopamine and norepinephrine–reuptake inhibitor) or aripiprazole (an atypical antipsychotic), as compared with a switch to bupropion, among older persons with depression who had not had a response to two courses of antidepressants. The authors found no evidence for a difference in effectiveness between augmentation with aripiprazole and augmentation with bupropion, but there was some evidence that both were more effective than a switch to bupropion. However, there was an important difference in adverse events among the trial groups. Aripiprazole was associated with a lower frequency of falls than bupropion augmentation. These findings therefore supported aripiprazole augmentation as being a potentially better overall strategy for older persons who have not had a response to conventional antidepressants. The percentage of patients who had remission in the aripiprazole-augmentation group was approximately 9 percentage points higher than in the switch-to-bupropion group. This modest benefit is worthwhile in this population, but overall outcomes were nevertheless still poor; only 29% of the patients in the augmentation groups had remission after treatment.

This trial makes an important contribution to the evidence regarding treatment-resistant depression in older adults. Older persons are often excluded from clinical trials of treatment for depression, which mostly involve younger adults. Findings from those trials are unlikely to be generalizable to older persons, who may have different symptoms of depression, more physical problems, cognitive impairment, polypharmacy, and a greater risk of adverse events.[1,2,4] For example, the average age of patients at baseline in this trial was 69 years, and 40% had had falls in the 6 months before enrollment.

The difference between trial groups in the rates of falls in the current trial is clinically relevant, given widespread concerns about this issue.[4] Aripiprazole augmentation was associated with 0.33 falls per patient, or one fall on average for every three patients during 10 weeks of treatment, as compared with 0.55 with bupropion augmentation. Although this difference in falls seems clinically meaningful, the upper boundary of the 95% confidence interval was close to 1 and may not exclude the possibility that there is little difference in the incidence of falls. In this older population, the rate of falls would be expected to be relatively high. In a population in which the rate of falls would be expected to be lower, this relative advantage could become less clinically important in absolute terms.

Bupropion was largely used in relatively high doses of 300 mg and 450 mg. A recent study has suggested that there is little clinical benefit in

increasing antidepressant doses above minimum recommendations,[5] although that study did not specifically examine bupropion. It is possible that smaller doses of bupropion than those used in the current trial would retain effectiveness while minimizing adverse effects such as falls. Lower doses of aripiprazole (up to 5 mg) might also retain effectiveness and minimize adverse effects.[4]

A common issue with clinical trials is the extent to which findings can be generalized to patients seen in clinical practice.[6] Although there was no upper age limit, the current trial mostly consisted of "younger older" adults. The trial also excluded persons with physical illnesses, so the results may also lack applicability to patients who are older and have complex medical problems. There is a risk of weight gain in patients prescribed antipsychotics such as aripiprazole, and, as is well known, this can be associated with metabolic syndrome, diabetes, and cardiovascular disease.[7] Aripiprazole generally causes less weight gain than other antipsychotics[8] — approximately 1 kg over 6 to 12 weeks.[7] Although most weight gain happens within 6 months after starting an antipsychotic, weight may accumulate with long-term use.

Findings from this trial support aripripazole augmentation as a strategy for treatment-resistant depression in older persons, largely because of the lower risk of falls than with bupropion augmentation. In clinical practice, however, it would be important to tailor treatment in light of potential adverse effects and the preferences of the patient. For example, akathisia is a common side effect of aripriprazole[5] and was reported in 11% of the patients who received the drug in this trial; patients may find this side effect distressing. How individual patients respond to different drugs for depression is also difficult to predict, so an element of trial and error is inevitable. It would be helpful to understand the mechanisms underlying the increased risk of falls with bupropion augmentation, because this could inform future treatment strategies. Augmentation of pharmacologic strategies with cognitive behavioral therapy could also be investigated in future studies involving older persons, as this has been an effective strategy for treatment-resistant depression in younger adults,[9] with benefits sustained over many years.[6]

Depression among older persons is often underrecognized or minimized, perhaps misattributed as a normal or inevitable part of aging.[1,4] Given the high prevalence of depression and the extent of nonresponses to first-line therapies, treatment resistance is a great clinical concern and has poor outcomes. The findings from this trial should help clinicians and older adult patients make informed decisions regarding the next steps, in the absence of a response to conventional pharmacologic approaches.

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From the Division of Psychiatry, Faculty of Brain Sciences, University College London, London.

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