Incomplete response in late-life depression: getting to remission

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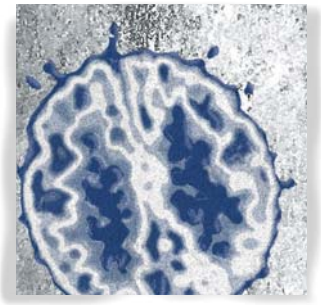

Incomplete response in late-life depression is an important public health problem

The aging of the US population is expected to increase the number of persons aged 65 and older from 35 million (in 2000) to more than 86 million by 2050.[1] These data, together with longer life expectancy and increased depression rates in recent cohorts,[2] predict an epidemic of late-life depression (LLD). LLD complicates medical illnesses[3-7] and increases mortality,[8] disability,[9] and health care utilization.[10] LLD often has poor acute

Incomplete response in the treatment of late-life depression is a large public health challenge: at least 50% of older people fail to respond adequately to first-line antidepressant pharmacotherapy, even under optimal treatment conditions. Treatment-resistant late-life depression (TRLLD) increases risk for early relapse, undermines adherence to treatment for coexisting medical disorders, amplifies disability and cognitive impairment, imposes greater burden on family caregivers, and increases the risk for early mortality, including suicide. Getting to and sustaining remission is the primary goal of treatment, yet there is a paucity of empirical data on how best to manage TRLLD. A pilot study by our group on aripiprazole augmentation in 24 incomplete responders to sequential SSRI and SRNI pharmacotherapy found that 50% remitted over 12 weeks with the addition of aripiprazole, and that remission was sustained in all participants during 6 months of continuation treatment. In addition to controlled assessment, evidence is needed to support personalized treatment by testing the moderating role of clinical (eg, comorbid anxiety, medical burden, and executive impairment) and genetic (eg, selected polymorphisms in serotonin, norepinephrine, and dopamine genes) variables, while also controlling for variability in drug exposure. Such studies may advance us toward the goal of personalized treatment in late-life depression.

Dialogues Clin Neurosci. 2008;10:419-430.

Keywords: *old-age depression; incomplete response; remission; pharmacologic augmentation; aripiprazole*

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Selected abbreviations and acronyms

LLD	*late-life depression*
SRNI	*serotonin/norepinephrine reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*
TRD	*treatment-resistant depression*
TRLLD	*treatment-resistant late-life depression*

outcome and brittle long-term outcome with antidepressant treatment.[11] Thus, new treatment approaches are needed to increase remission from LLD and to support evidence-based selection of appropriate interventions at different points in the course of illness (ie, the right treatment at the right time).

Treatment-resistant depression (TRD) has been defined as failure to achieve remission with one antidepressant medication trial,[12-14] or two trials,[15] of adequate dose and duration. Rates of treatment resistance in randomized controlled trials in LLD are as high as 77% using selective serotonin reuptake inhibitors (SSRIs)[16] and range from 55% to 81% using serotonin/norepinephrine reuptake inhibitors (SNRIs).[16-19] Treatment resistance must be distinguished from inadequate treatment (eg, short treatment duration preventing late responders from achieving remission), and misdiagnosis (eg, failing to recognize dementia, psychosis, or bipolar disorder). Treatment resistance is particularly germane to LLD, for three reasons. First, high rates of *comorbid anxiety and medical illness* contribute to treatment failure. Second, older adults may have greater *pharmacodynamic variability* as a result of *genetic variability* (eg, at serotonin receptors[20]) and *age- or medical illness-related changes in brain structure or function* (eg, decline in serotonin receptors[21,22]), interruptions in neurocircuitry integrity from cerebrovascular disease or prodromal Alzheimer's disease.[23,24] Third, older adults may have greater *pharmacokinetic variability*, as a result of poor adherence (eg, due to cognitive impairment) and metabolic variability (eg, due to age-related changes in drug metabolism).[25]

The serious consequences of persistent depressive symptoms in elderly persons include relapse and recurrence,[26-29] functional disability,[30] and cognitive decline, owing in part to the impact of long periods of untreated depression on hippocampal volume.[31] Persisting LLD is also associated with an increased mortality,[32] including suicide. Risk for suicide can be reduced with successful treatment.[33,34] Finally, treatment-resistant late-life depression (TRLLD) is associated with increased caregiver burden in family members of depressed elders (Martire L, personal communication, 2008). In these ways, incomplete response in late-life depression and the need to get to remission are major public health challenges.

Despite this challenge, almost no data exist to guide the treatment of TRLLD. The best current evidence guiding intervention for treatment-resistant depression comes from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D study[35]). However, only a small minority of subjects who participated in STAR*D were elderly. Our collaborative group has carried out several examinations of treatment strategies for TRLLD, including open studies of switching from an SSRI to nortriptyline,[36] venlafaxine,[37] or duloxetine,[38] a stepwise strategy of bupropion, nortriptyline, or lithium augmentation of SSRI,[39,40] and electroconvulsive therapy.[41,42] Our findings suggest that a significant proportion (40% to 50%) of SSRI nonresponders will respond to these strategies, consistent with a prior open sequential trial.[43] In the only published placebo-controlled pharmacotherapy trial for TRLLD, Sunderland et al[44] found that the monoamine oxidase inhibitor (MAOI) selegiline was efficacious. However, in a recent randomized comparison of lithium augmentation and the MAOI phenelzine for TRLLD, one third of those receiving lithium remitted versus none receiving phenelzine.[19] These two controlled studies suffer from small sample size, short duration, and inclusion of subjects with psychosis. Thus, beyond the intuitive step of switching from SSRI to SNRI, there appear to be almost no controlled data to inform the treatment of TRLLD in old age.

The relationship of anxiety, comorbid medical illness, and executive dysfunction to TRLLD

Literature reviews have suggested that anxiety, medical illness, and executive dysfunction may be key clinical predictors of treatment resistance in LLD.[37,45]

Anxiety

Anxiety is a common cotraveler with LLD. Several studies have found an increased time to remission, and reduced remission rate, in LLD when there are either high levels of anxiety symptoms[46-52] or a comorbid anxiety disorder such as generalized anxiety.[53] Despite numerous studies establishing anxiety as a predictor of treatment resistance in LLD, this relationship is poorly understood. Mechanisms that may explain this relation-

ship include reduced tolerance of, and adherence to, medication, or a more severe subtype of depression. Anxiety in late life is multidimensional, encompassing worry, panic/fear, somatization, and personality factors[54]; the differential impact of these dimensions on treatment resistance is largely unstudied. Along these lines, we have found preliminarily that symptoms of worry, and not fear or panic, predict both poor short-term outcome in LLD and poor long-term stability of remission (Andreescu C, personal communication, 2008). Needed is a treatment trial incorporating examinations of these multiple dimensions that will shed light on the anxiety-depression interface in late life.

Medical burden

Several studies have demonstrated that LLD patients with greater medical burden have a lower, and slower, treatment response in LLD (eg, refs 55-57). Although some studies have not supported a link between medical burden and treatment outcome,[58,59] our group found that greater medical burden predicted poorer acute outcome to antidepressant augmentation (primarily with bupropion or nortriptyline[40]) and poorer maintenance outcomes.[60] One reason may be that medical illnesses seen in patients with LLD (eg, hypertension, high cholesterol, diabetes, endocrinologic disease) induce pharmacodynamic or structural central nervous system changes that reduce the efficacy of standard antidepressants. Other possibilities are that medical burden interferes with antidepressant adherence and/or increases variability of drug exposure, thus reducing the impact of antidepressants.

Impairment of executive functioning

Neuropsychological impairment, particularly in executive functioning, is common and clinically significant in LLD.[61] Several studies have noted a relationship of cognitive impairment with lower antidepressant response rates,[62-64] though other studies have not found this relationship.[65-67] The discrepancy may result from the variability between studies in measuring executive functioning, and the current consensus in the field is that executive dysfunction is associated with poorer LLD treatment outcomes with antidepressants. Treatment resistance in the context of executive dysfunction is thought to be due to alterations in neurocircuitry integrity that disrupt the pharmacodynamics of antidepressants.[68]

In summary, the above clinical variables predict poor antidepressant outcomes in LLD. However, there is insufficient understanding of how they contribute to poorer outcomes, and so their clinical utility is limited. This lack of understanding is part of the gap between personalized medicine (matching treatment to patients based upon patient characteristics) and the current trial-and-error approach to LLD management.

The relationship of genetic and drug exposure variability to TRLLD

Functional genetic polymorphisms change the pharmacodynamics of antidepressant medications; therefore, it is posited that antidepressant outcomes in LLD can be predicted by genetic variation in their homologous receptor targets.[69] In other words, functional genetic variation of the 5-HTT is expected to affect SSRI response, while variation in the norepinephrine transporter (NET) is expected to affect SNRI response. One example is the serotonin transporter linked polymorphic region (5-HTTLPR) in the promoter of the gene that encodes for the serotonin transporter (5-HTT), the primary target of SSRIs. A deletion polymorphism in 5-HTTLPR, the s allele (s="short" vs l="long"), appears to be functional: it reduces expression of 5-HTT so that individuals with the s allele have fewer 5-HTTs than those with l/l genotype. The association of the s allele with poorer SSRI outcomes has been demonstrated in LLD,[70] including a study from our group that was the first to report this association in LLD.[20] The association appears specific to SSRIs and was not found with mirtazapine[71] or nortriptyline.[70]
In addition, we think that measures of drug exposure are needed to interpret clinical and genetic findings.[72] Specifically, we think that pharmacokinetic modeling is important in pharmacogenetic analyses. Supporting this contention, Lotrich et al[73] found that the 5-HTTLPR s allele predicted poorer treatment outcome at lower concentrations of paroxetine but not at higher concentrations.
Following up on this observation, Lotrich examined depressed elderly subjects who were treated in an open-label paroxetine study and who were genotyped (n=110). Again, there was an interaction between paroxetine concentration and 5-HTTLPR genotype on symptomatic improvement over 12 weeks ($F(18,59.5)=1.8$; $P<0.05$): paroxetine concentrations were correlated with change in the Hamilton Depression Rating Scale (HAM-D) in

subjects with the s allele, but not in subjects homozygous for the l allele. In other words, the s allele moderated the impact of the drug. These data demonstrate the importance of pharmacokinetic data for conducting meaningful pharmacogenetic analyses. This issue is particularly relevant to geriatrics, as age-related changes in drug elimination amplify drug concentration differences for a given dose.

Relevance of anxiety, medical burden, executive dysfunction, and genetic variability for augmentation strategies in TRLLD

Comorbid anxiety, medical burden, and executive dysfunction are highly prevalent in TRLLD patients. Because these variables are associated with poor outcomes using standard antidepressants, they may identify patients likely to require more aggressive strategies including augmentation (as opposed to "staying the course"). As such, these variables are expected to moderate the efficacy of augmentation (ie, increase drug-placebo difference). This is consistent with research from PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) in which executive dysfunction moderated the difference between aggressive LLD management and usual care.[74] A similar moderation effect has been found with medical comorbidity[60,75] and comorbid anxiety.[9] Thus, we hypothesize that anxiety, medical burden, and executive dysfunction are clinical markers of need for augmentation.

Conversely, it is possible that these variables predict treatment nonadherence or increased metabolic variability resulting in poor outcomes regardless of treatment.[40] This possibility underscores the importance of measuring drug exposure in studies of TRLLD. For example, by controlling for both the average drug concentration and the variability of drug exposure, it is possible to determine the contribution of comorbid medical illness to treatment efficacy while accounting for drug exposure. The same logic applies for patients with highly prevalent genetic polymorphisms. Thus, by using drug exposure data the effect of clinical and genetic moderators can be more precisely examined, ultimately reducing the gap between the potential of personalized medicine and the current empiric approach for LLD management. In the next section, we present for heuristic purposes our work with aripiprazole as a candidate augmentation strategy for managing incomplete response in LLD and getting to remission. We present first a pharmacologic and clinical rationale, followed by pilot data. Finally, we describe the design of a randomized controlled trial informed by those data.

Aripiprazole as a potential treatment for TRLLD

Aripiprazole is an atypical antipsychotic (or "atypical") approved by the Food and Drug Administration to treat schizophrenia and mania. It has a high D_2 receptor affinity, and as a partial agonist, it has a higher affinity for the G protein-coupled state of the D_2 receptor, ie, its active state.[76] With partial D_2 agonist properties it is conceived as a dopamine system stabilizer: in high dopaminergic states it acts as an antagonist, and in low dopaminergic states it acts as an agonist.[77] This may explain why it is unlikely to cause extrapyramidal side effects or prolactin elevation even at high D_2 receptor occupancy.[78-80] Aripiprazole also has high affinity for the D_3 receptor and is an antagonist at the 5-HT_{2a} receptor.[81] It has only moderate affinity to the adrenergic alpha-1 receptor and histamine H_1 receptor, and negligible affinity to the muscarinic receptor.[82] As a result, orthostatic hypotension and antihistaminergic or anticholinergic adverse effects are less likely to occur than with other atypicals. Also, increases in mean QTc interval are not observed. Finally, as hyperprolactinemia can contribute to osteoporosis, aripiprazole's lack of this side effect reduces this concern. These pharmacodynamic features make aripiprazole attractive for use in older patients.

A meta-analysis of the use of atypicals as augmentation treatment for depression found pooled response rates of 57% vs 35% for placebo.[83] The meta-analysis utilized data from 10 double-blind, placebo-controlled studies of augmentation of an antidepressant with an atypical antipsychotic agent. Augmentation with olanzapine, risperidone, and quetiapine was found to be efficacious for treatment-resistant depression. This meta-analysis did not include data on aripiprazole or from geriatric samples. In part, the efficacy of atypicals in this context seems to stem from their benefit for anxiety,[84,85] which is a marker for poor outcomes in MDD. Their 5-HT_{2a} receptor antagonism would be expected to increase serotonin and norepinephrine release, thus augmenting the effect of SSRIs and SNRIs.[86,87] In the case of aripiprazole, antidepressant and antianxiety actions could also stem from its D_2 partial antagonism[88] or its high affinity for D_3

receptors. A novel neurobiological paradigm views anxiety and depression in the context of the amygdala-prefrontal circuit, with amygdala hyperactivity coinciding with prefrontal hypoactivity[89] and both coinciding with imbalances in dopamine.[90] Aripiprazole, through its dopamine partial agonism, may promote equilibrium in this circuit and provide benefits for anxiety and depression. However, this neurobiological argument requires further testing.

Two large, industry-initiated, placebo-controlled trials of nongeriatric adults have recently demonstrated the efficacy of aripiprazole as an augmentation treatment for depression incompletely responsive to SSRIs and SNRIs.[91,92] Based on these regulatory trials, the FDA has approved an indication for the use of aripiprazole to augment SSRIs and SNRIs for treatment-resistant depression. The one published trial showed a higher rate of remission (as measured with the Montgomery-Åsberg Depression Rating Scale) in the aripiprazole group than in the placebo group. Few adverse events leading to about 3% discontinuation in each group.[91,92] Two limitations of this study were the short duration of the augmentation trial (6 weeks) and the high placebo remission rate (37%) suggesting that the criteria for treatment resistance (failure to respond to one 8-week antidepressant lead-in phase that did not maximize dosage) were not stringent enough.

Aripiprazole has been examined preliminarily in LLD as an augmentation for SSRI nonresponders,[93] and the Pittsburgh group has examined its effect and tolerability in 24 SNRI nonresponders[94] (data presented below). As described below, these two small open-label studies have similar results: 50% of older nonresponders converted to remitters, and adverse events requiring treatment cessation were infrequent. These preliminary results are encouraging but, to our knowledge, no placebo-controlled examination of aripiprazole for TRLLD has been carried out.

Safety issues with atypicals in older adults

Atypicals have come under scrutiny due to the metabolic disturbances they may cause and safety issues uncovered in older patients with dementia. Weight gain and related metabolic disturbances such as glucose intolerance and dyslipidemia occur more frequently in psychiatric patients than the general population, with the totality of risk related not only to medication effects but to underlying characteristics of the patient population (eg, baseline overweight and obesity, high fat/high caloric diet, poor medical care).[95] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) confirmed other reports demonstrating risks for metabolic disturbances with atypicals, although that study did not examine aripiprazole. Among the atypicals, risk of weight gain, dyslipidemia, and diabetes is highest with clozapine and olanzapine; more modest weight gain is generally observed with quetiapine and risperidone, along with lower insulin resistance risk, variably lower dyslipidemia risk, and largely negative if somewhat discrepant results concerning diabetes risk. The lowest risk of weight gain, as well as little or no risk for dyslipidemia or diabetes, is observed with aripiprazole and ziprasidone.[95-97] These metabolic risks have not been consistently reported in the elderly, where some studies indicate little or no weight gain, even on higher-risk agents (eg refs 98-100). However, there are limited data in elderly samples, and available reports that include a placebo group often find weight loss, consistent with progressive reductions in lean muscle mass. Thus, in elderly persons, measuring weight gain alone with antipsychotics could miss treatment-related increases in adiposity. Direct measures of adiposity such as dual-energy X-ray absorptiometry (DEXA) as well as sensitive and reliable measures of insulin resistance, lipid metabolism, and glucose control, are needed in research studies of these medications to examine metabolic risk.

A meta-analysis found a higher mortality with atypicals compared with placebo in older patients with dementia, resulting in a black-box warning for the entire class of atypicals. It remains unclear what the increased mortality resulted from, though possibilities include the sedating properties of these agents (leading to falls or aspiration pneumonia), QT prolongation (leading to arrhythmias and sudden cardiac death), venous thromboembolism leading to pulmonary embolism, and other cardiovascular or cerebrovascular events.[101,102] It is unknown whether these risks apply to nondemented elderly patients. A third type of adverse event involves extrapyramidal side effects and other (nonvascular) neurological problems. Age-associated reductions in dopamine and D_2 receptors make the elderly more sensitive to antipsychotics, although aripiprazole's partial agonism at the D_2 receptor could reduce such effects. Thus, a placebo-controlled clinical trial is needed to further investigate the tolerability and safety of aripiprazole

augmentation in LLD. The lack of such a trial is a significant gap in our knowledge base.

In summary, TRLLD is a common and potentially devastating condition, yet we have an extremely limited evidence basis for its management. Clinicians do not have data to guide them regarding which augmentation agent to use, in whom, how, or with which risk:benefit ratio. Needed is a randomized placebo-controlled trial to support the value of a modern pharmacologic treatment for TRLLD, to establish a new approach to TRLLD, to lead to a greater understanding of treatment response variability and ultimately to personalized treatment for LLD. Also needed is a multidimensional approach to treatment resistance, in which key clinical features in LLD (anxiety, medical comorbidity, and executive dysfunction) are examined as hypothesized moderators for augmentation outcomes. An examination of genetic variability at the drug target molecules, with a goal to predict those in whom specific treatment strategies (eg, high-dose venlafaxine, aripiprazole augmentation) are more robust is also needed to personalize treatment. Finally, a detailed examination of the sources of treatment resistance using state-of-the-art pharmacokinetic methods is necessary. For illustrative purposes, we now present work in progress with aripiprazole as a candidate augmentation strategy for incomplete response to antidepressant pharmacotherapy.

Aripiprazole augmentation data: pilot study and design of a controlled trial

To examine the acceptability, feasibility, and safety of aripiprazole as an augmentation agent for incomplete response in LLD, we carried out a 12-week open-label pilot study in 24 elderly patients.[94] Patients aged 65+ with current major depressive disorder, with an initial HAM-D score ≥5 were first treated with escitalopram for 16 weeks. Those who failed to respond (HAM-D≥15, N=19) or responded partially (HAM-D=11-14, N=5) were switched to either duloxetine up to 120mg/d or venlafaxine up to 225 mg/day (depending on tolerability and prior medication history) and treated for 12 weeks. Those with partial or nonresponse to the SNRI were started on 2.5 mg/day of adjunctive aripiprazole, titrated weekly in 2.5-mg increments to 15 mg, as tolerated and as needed to reach remission.

The 24 subjects had a mean age of 74 (range 65 to 91); 58% were female; 8% were African-American. Nineteen of 24 (79%) patients completed all 12 weeks of augmentation with aripiprazole, and 12/24 (50%) met criteria for remission (defined as 2 consecutive weeks of HAM-D≤10).

Tolerability and side effects

Three of 24 (13%) discontinued prior to week 12 due to failure to improve or withdrawal of consent, and 2/24 (8%) discontinued due to side effects (one each: sedation, akathisia). Side effects were also examined via the UKU side effects scale.[103] Overall UKU scores showed a decline (indicating fewer reports of somatic complaints compared to baseline). However, the mean score of the UKU-Neurologic subscale increased. Six of 24 (25%) subjects had a positive score on the UKU-akathisia item on at least one time point; however, in all but one case, these were mild and/or transient.

We also examined metabolic changes and weight gain during the 12-week period of pharmacotherapy augmentation. One subject had a significant increase in lipids, and none had a significant increase in blood sugar, suggesting that metabolic effects were infrequent with aripiprazole. Weight gain was highly variable: 9/15 (60%) gained <2 kg (mean [range] 0.8 [-0.7- 1.8]) while 6/15 (40%) gained >3 kg (mean [range] 4.7 [3.2-6.4]), suggesting that an examination of sources of weight gain variability would be useful. Two possibilities from the literature are genetic variation at the 5-HT_{2C} receptor (posited as the receptor responsible for weight gain with aripiprazole) and baseline body mass index (BMI). Also, we were not able to determine whether weight gain represented an increase in adiposity vs an increase in lean body mass with remission from depression. Thus, we determined that a controlled study should include: (i) a more precise examination of changes in adiposity, including DEXA scans which would provide quantitative measures of body fat; (ii) an examination of moderators of weight gain (including baseline BMI and 5-HT_{2C} genotyping); and (iii) a continuation phase, allowing longer duration to observe weight changes.

Pilot study of continuation phase pharmacotherapy

Of the 24 participants who received acute-phase adjunctive aripiprazole, 12 met study criteria for complete response (remission) and entered continuation phase pharmacotherapy, on an average daily dose of 10 mg of

aripiprazole (as an adjunct to their primary antidepressant pharmacotherapy). The 12 participants in the feasibility study of continuation-phase pharmacotherapy had a mean age of 72.7 (SD: 6.2); 9 were women, and 10 were white (2 were African-American).

Outcomes

Depressive relapse during continuation-phase pharmacotherapy

Over a median duration of 27.6 weeks (range: 2-106) of continuation-phase combined pharmacotherapy (antidepressant + aripiprazole), none of the 12 participants experienced relapse of a major depressive episode.

Retention

One of 12 participants was noncompliant with study procedure (due to respondent burden and other treatment preferences) and exited the study.

Side effects

UKU side effect scores remained stable (9.4[3.2] at start of continuation-phase pharmacotherapy [n = 12] and 7.9[2.8] at 6 months [n = 7]). No participant left the study due to treatment-emergent adverse events.

Metabolic data

Body mass index was stable over 6 months (29.8 [6.1] at start of continuation phase pharmacotherapy [n = 12] and 30.1 [6.1] at 6 months [n = 7]).
Figure 1 depicts individual participants' patterns of change in the metabolic data between baseline and 6 months, after an overnight fast for glucose, triglyderides, cholesterol, HDL, and LDL. In general, values were stable over time. One person each had a spike in glucose, triglycerides, and cholesterol/LDL. After the 6-month follow-up, this last person was started on a statin prescribed by their primary care physician, who judged that the benefit of continuing treatment with aripiprazole in the study was substantial, and that metabolic changes could be managed medically.
In general, glucose and triglycerides showed minimal change, suggesting that aripiprazole does not cause insulin resistance as do some other atypicals do (eg, olanzapine). In a comprehensive review of this topic, Newcomer showed that generally a lipid signal with atypicals will be seen in triglycerides; thus the lack of a signal in these pilot data suggest that aripiprazole will be a safe treatment in older adults with respect to metabolic effects.[97] We plan to closely control the collection procedures in subjects, so that pre-post differences are not due to variability in fasting, stasis-venous collection, etc. The lack of clinically informative data on this in the elderly is striking in light of the high cardiovascular mortality in mentally ill persons generally and underscores the need for this research.[104]
These data from acute and continuation open pharmacotherapy illustrate three points.

1. Further investigation should evaluate *both* the benefits and the costs (eg, adverse effects, metabolic changes) of adjunctive aripiprazole pharmacotherapy, using a double-blind, randomized, placebo-controlled design.
2. These data show the *feasibility* and *safety* of treating participants (i) during acute-phase pharmacotherapy (n=24), to determine change from incomplete to complete response; and (ii) during continuation-phase pharmacotherapy (n=12), to determine stability of remission and rates of depressive relapse.
3. These data also underscore the *importance* of examining risks, as well as benefits, in a large randomized, double-blind, placebo-controlled study. The cost-benefit ratio and the ensuing clinical conclusions may be very different when benefit and harm are conjointly considered, from what they are when benefit and harm are considered separately (as the post-marketing experience with COX-2 inhibitors and oral hypoglycemic agents teaches us, vis-à-vis heart disease). We believe that this is the most appropriate approach scientifically and ethically to a treatment study of frail older depressed patients who have responded only partially to antidepressant pharmacotherapy.

Our conclusions from this pilot study

1. In older adults with MDD having incomplete response to an SSRI followed by an SNRI, remission was obtained in 50% during aripiprazole augmentation.
2. In most subjects who remitted, the improvements in depression were stable throughout 6-month continuation pharmacotherapy.
3. Aripiprazole was well-tolerated, with a low rate of dropout due to side effects and a high completion rate,

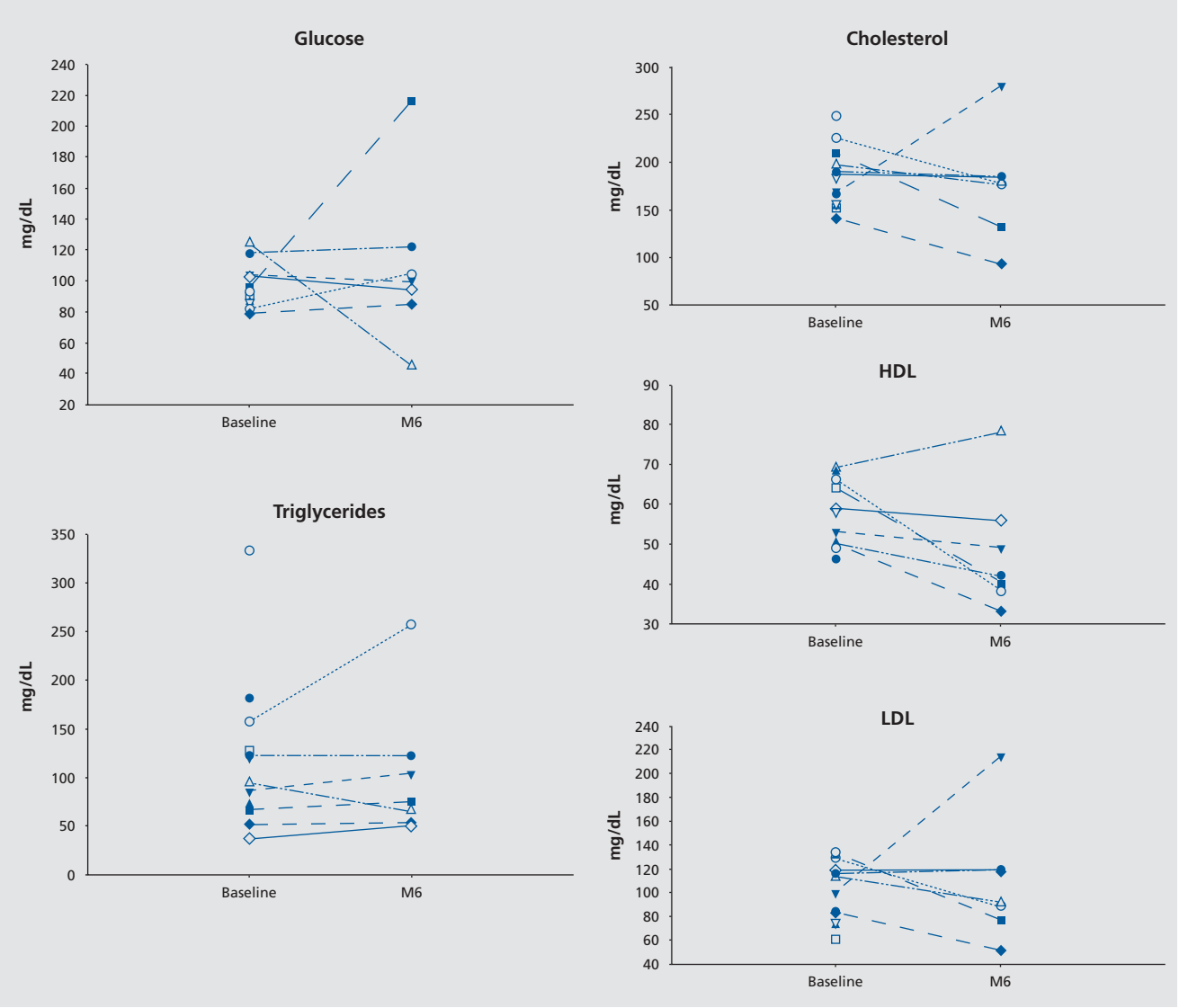

Figure 1. Metabolic profile of individual patients (each indicated by a separate symbol) during continuation treatment with aripiprazole over a median period of 6 months.

but restlessness and weight gain were not uncommon. Overall, a larger, placebo-controlled study is needed to test hypotheses related to remission, tolerability, safety, and outcome predictors. These pilot data support the feasibility of such a trial. In *Figure 2*, we show the design of a placebo-controlled randomized clinical trial which we plan to conduct.

The planned trial calls for enrolling 500 patients aged 60 and older with major depressive disorder and treating them openly for 12 weeks with venlafaxine XR (up to 225 mg/d) to prospectively determine incomplete response (phase 1). Participants meeting criteria for incomplete response estimated (n=200) will be randomly assigned to receive either aripiprazole (2.5-15 mg/d; target dose: 10 mg/d) or placebo augmentation of venlafaxine for 12 weeks (phase 2), with the goal of achieving remission (Montgomery-Åsberg DRS<10 for two consecutive assessments). Those who remit in phase 2 will receive continuation treatment, with the same double-blinded intervention to which they were randomly assigned (phase 3), for 12 weeks to determine the stability of remission. Based on efficacy and tolerability data,

we will estimate number needed to treat and number needed to harm, providing a clinically informative estimate of benefits and risks of aripiprazole augmentation for TRLLD.

Conclusion

In summary, the public health importance of TRLLD studies is great, but there are no data from controlled studies to guide practice. Data are needed to not only examine the overall efficacy of adjunctive treatments but also examine in whom such treatments are most efficacious and safe, thus moving the treatment of LLD into the arena of personalized medicine. ❑

Acknowledgments: P30 MH071944, R37 MH43832, R01 MH3786769, T32 MH19986, RR 024153, and the John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry

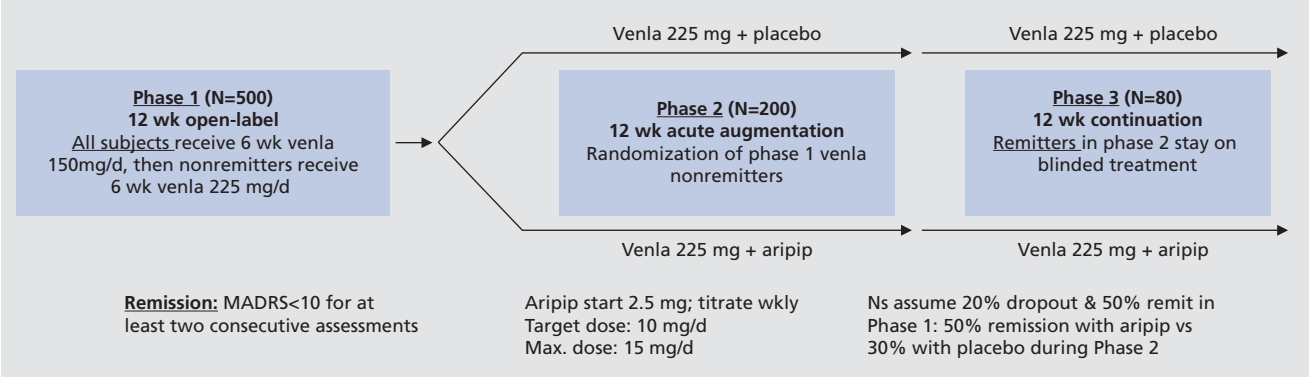

Figure 2. Representation of proposed multisite study of aripiprazole (aripip) augmentation for treatment-resistant late-life depression. Venla, venlafaxine

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Respuesta incompleta en la depresión del anciano: alcanzando la remisión

La respuesta incompleta del tratamiento de la depresión del anciano es un gran desafío para la salud pública: al menos un 50% de las personas de edad avanzada no responden adecuadamente a la farmacoterapia antidepresiva de primera línea, aun bajo condiciones terapéuticas óptimas. La depresión resistente al tratamiento en el anciano aumenta el riesgo de una recaída precoz, reduce la adherencia al tratamiento de los trastornos médicos coexistentes, amplifica la incapacidad y el deterioro cognitivo, impone una mayor carga para los cuidadores de la familia y aumenta el riesgo de mortalidad precoz, incluyendo el suicidio. Alcanzar y mantener la remisión es el objetivo primario del tratamiento, pero hay una carencia de datos empíricos acerca del mejor manejo de este tipo de depresión. Un estudio piloto realizado por nuestro grupo con aripiprazol como potenciador en 24 respondedores incompletos a una secuencia de farmacoterapia con ISRS y antidepresivos duales encontró que el 50% remitió en 12 semanas con la adición de aripiprazol, y que la remisión se mantuvo en todos los participantes durante los 6 meses de continuación del tratamiento. Además de la evaluación controlada, se necesita contar con evidencia que sustente el tratamiento personalizado mediante el análisis del papel moderador de variables clínicas (como ansiedad comórbida, costos médicos y deterioro ejecutivo) y genéticas (como determinados polimorfismos de genes para serotonina, noradrenalina y dopamina), y también el control de la variabilidad en la exposición a drogas. Tales estudios pueden hacernos progresar hacia el objetivo del tratamiento personalizado de la depresión del anciano.

Réponse partielle dans la dépression du sujet âgé : vers la rémission

La réponse partielle dans le traitement du sujet âgé est un défi majeur de santé publique : 50 % environ des personnes âgées ne répondent pas correctement au traitement antidépresseur de première intention, même en conditions thérapeutiques optimales. La dépression tardive résistant au traitement (DTRT) augmente le risque de récidive précoce, diminue l'observance au traitement de troubles médicaux coexistants, majore l'invalidité et les troubles cognitifs, impose une lourde charge à la famille proche et augmente le risque de décès précoce y compris de suicide. Le premier but du traitement est d'obtenir et de prolonger la rémission, malgré l'absence de données empiriques sur la meilleure façon de prendre en charge la DTRT. Notre groupe a mis en place une étude pilote sur l'ajout d'aripiprazole chez 24 répondeurs partiels au traitement séquentiel par IRSS et IRSN et a trouvé que 50 % des patients étaient en rémission dans les 12 semaines suivant l'addition d'aripiprazole, avec prolongation de la rémission pendant les 6 mois de traitement continu pour tous les participants. En plus de l'évaluation contrôlée, des données complémentaires sont nécessaires afin de proposer un traitement personnalisé en vérifiant le rôle modérateur des variables cliniques (anxiété comorbide, charge médicale, et détérioration exécutive) et génétiques (sélection des polymorphismes des gènes de la sérotonine, de la norépinéphrine et de la dopamine), tout en luttant aussi contre la variabilité de l'exposition au produit. De telles études peuvent nous faire avancer afin de trouver un traitement personnalisé de la dépression du sujet âgé.

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