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Notice of Correction: References 13 and 14 have been transposed: reference 13 is now Stahl and reference 14 is now Resler et al.

Combining Antidepressant Therapies From the Initiation of Treatment: A Paradigm Shift for Major Depression

Stephen M. Stahl, MD, PhD

Issue: *Combining 2 therapeutic agents from the very initiation of treatment for major depression may lead to enhanced outcomes compared to treatment with a single antidepressant.*

Antidepressants can be life saving, but only about a third of patients attain full remission of their symptoms with their first treatment, and many of these patients relapse despite continuing treatment.[1] Treatment guidelines for major depression generally call for starting a single "first-line" agent and then trying a series of other single agents if the first one is not tolerated or is relatively ineffective.[1] Second and subsequent treatments are progressively less likely to lead to full remission of symptoms, and for those treatments that do lead to remission, they are progressively less likely to sustain that remission for more than a few months.[1] In order to target greater sustained remission rates from a major depressive episode, a paradigm shift is afoot in which the chances of a first treatment working are maximized by giving combinations of treatments from the time the first antidepressant therapy is initiated (eTable 1).[2]

Are 2 or More Therapeutic Mechanisms Better Than 1?

Some antidepressants have a single major mechanism of therapeutic action, and others have 2 or more.[1–6] These latter drugs are sometimes called multifunctional, with recent theories suggesting that multiple mechanisms of antidepressant action in a single drug are better than a single mechanism.[3–7] Multifunctional actions can also be created by combining 2 drugs with clearly different mechanisms. Numerous investigations are now ongoing to determine whether, from the initiation of antidepressant therapy, the combination of drugs works better than either agent alone.[2,8–18]

Antidepressants Plus Antidepressants

The landmark study by Nelson et al[8] showed that the combination of the SSRI (selective serotonin reuptake inhibitor) fluoxetine with the norepinephrine reuptake inhibitor desipramine in non–treatment-resistant inpatients with a major depressive episode was significantly more likely to result in remission than was fluoxetine alone or desipramine alone.[8] Blier et al[9,10] are also conducting a series of very novel studies of antidepressant combinations, showing in 1 study that remission rates of patients taking the SSRI paroxetine + mirtazapine were double the rates of those taking the single drugs.[9] Further studies by this group suggest that remission rates with several combinations of antidepressants also roughly doubled the remission rates with a single agent (specifically, mirtazapine + either fluoxetine, venlafaxine, or bupropion vs fluoxetine alone).[10] These very promising findings are now being followed up by a major study funded by the NIMH Combining Oral Medications to End Depression (COMED) on the Depression Trials Network comparing the potential benefits of combining any 2 of the agents at initiation of treatment: bupropion, escitalopram, mirtazapine, or venlafaxine. If these results replicate the doubling of remission rates, there will most likely be a rapid shift to using 2 agents from initiation of treatment for a major depressive episode.

Antidepressants Plus Methylfolate/Folate

One of the first agents conceptualized to be a combination therapy from the initiation of treatment of major depression was the natural product folic acid and its centrally active natural derivate methylfolate. Three randomized controlled trials[11,12,14] have shown superior efficacy of antidepressant and folate/methylfolate combinations from initiation of therapy compared to antidepressants alone.

In the first such study,[11] depressed patients specifically with low red blood cell (RBC) folate levels were given treatment as usual in the pre-SSRI era and randomized to either 15 mg/d of racemic methylfolate or placebo from the initiation of therapy. Serum and RBC folate levels increased, and clinical measures of mood improved significantly more in the antidepressant + methylfolate group

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From the Neuroscience Education Institute in Carlsbad, California, and the Department of Psychiatry at the University of California San Diego.

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than in the antidepressant monotherapy group.

A second study[12] randomized patients with major depression to the SSRI fluoxetine + 0.5 mg of folate or to fluoxetine alone. Not surprisingly, plasma folate levels rose, especially in women, but plasma homocysteine levels[13] (which L-methylfolate converts into methionine and then *S*-adenosylmethionine) declined only in women. Patients taking fluoxetine + folate had significantly more improvement in depression than patients taking fluoxetine alone, but this change was accounted for entirely by the women who improved. The authors suggested that folate be dosed sufficiently to show a physiologic effect, namely lowering of homocysteine levels in order to optimize potential antidepressant actions.[13] As 0.5 mg of folate is a much lower dose than the equivalent dosing of the first study,[11] this suggestion seems reasonable (ie, 15 mg of racemic methylfolate is equivalent to 7.5 mg of the naturally occurring active form L-methylfolate, which is equivalent to 52 mg of folic acid[13]).

The third controlled study[14] of antidepressant + folate/methylfolate combination from the start investigated fluoxetine + 10 mg of folate or fluoxetine + placebo. Patients receiving folate showed decreased homocysteine levels, and they also had significantly lower depression scores compared with the fluoxetine monotherapy group.

A study of a large population of depressed patients receiving either high doses of the centrally active L-methylfolate, 7.5–15 mg, added to SSRI treatment from the start or SSRI monotherapy is ongoing, with measurement of folate and homocysteine levels. If this study confirms the others, it may provide clearer guidelines on potential dosing of the centrally active L-methylfolate for us in antidepressant treatment combination from the start.

Antidepressants Plus Hypnotics

A surprising set of results has come from the innovative study of Fava et al[15] in which patients with major depression and insomnia were treated from the start with either fluoxetine + the hypnotic eszopiclone or with fluoxetine alone. As expected, the patients receiving the hypnotic with the antidepressant had better sleep scores, but what was unexpected is that they also had better improvement in other depression symptoms and significantly increased remission rates. This finding of enhanced remission rates beyond just improvement in sleep has been replicated in another group of patients with generalized anxiety disorder receiving a different SSRI, escitalopram, + either eszopiclone or placebo.[16]

It is not clear whether the enhancement of antidepressant remission rates by eszopiclone is a class action for any hypnotic or selective for this specific hypnotic, as these results were not replicated by the same group using zolpidem.[17] However, the sleep-enhancing effects of other hypnotics have long been suspected to enhance antidepressant efficacy when added to antidepressants, including the 5-$HT_{2A/2C}$ antagonist trazodone,[6] the melatonergic agonist agomelatine,[18] and the atypical antipsychotic with potent antihistamine properties, quetiapine and its active metabolite norquetiapine[1,7]

Conclusion

Evidence is reaching the tipping point where combination therapy from the initiation of treatment for major depression may begin to replace a series of consecutive monotherapies to obtain the best outcomes. ◆

Take-Home Points

- Traditional treatment of major depression begins with a single "first-line" antidepressant; augmentation by a second agent occurs only after 1 or more single agents fail.
- Evidence is accumulating now that patients starting combination therapy from the very initiation of treatment for major depression may experience enhanced outcomes, attaining higher remission rates and lower relapse rates than with single antidepressants.
- Starting rather than ending with a multifunctional pharmacologic approach to major depression by utilizing more than 1 therapeutic agent would represent a major paradigm shift in the treatment of depression.

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