

Enhancing Outcomes from Major Depression: Using Antidepressant Combination Therapies with Multifunctional Pharmacologic Mechanisms from the Initiation of Treatment

Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

Traditional guidelines call for treatment of major depression with a sequence of single antidepressants. Augmentation with a second agent generally only occurs when the first agent is well tolerated and when it also provides at least some symptomatic improvement on its own. Since this standard approach leads to low rates of attaining and sustaining remission by the first agent, with diminishing returns for each subsequent agent, there is growing dissatisfaction with this approach to the treatment of major depression. One new trend is to attempt to enhance the rates of sustained remission from a major depressive episode by combining two therapeutic agents from the very initiation of treatment of a major depressive episode.

THE PROBLEM: TREATMENTS YIELD LOW SUSTAINED REMISSION RATES IN DEPRESSION

Traditional treatment of major depression begins with a single “first line” antidepressant, and if it does not work or is not tolerated, trying another and then another.^{1,2} Unfortunately, this strategy results in disappointing remission rates for the first antidepressant (Figure 1),^{2,3} and disappointing rates of maintaining any improvement that is attained by this first agent because of high relapse rates over the next year despite continuing treatment with the first antidepressant (Figure 2A).^{2,4} And that is the good news. The bad news is that with each subsequent antidepressant treatment administered remission rates are progressively reduced (Figure 1).^{2,3} For those patients who do improve, they are progressively less likely to sustain their therapeutic gains despite continuing to take the drug that led to their initial improvement (Figure 2).^{2,4}

Dr. Stahl is adjunct professor of psychiatry in the Department of Psychiatry at the University of California—San Diego in La Jolla and Honorary Visiting Senior Fellow at Cambridge University in the United Kingdom.

Faculty Disclosures: Dr. Stahl has served as a consultant to Arena, Azur, Bionevia, Bristol-Myers Squibb, Eli Lilly, Endo, Forest, Jazz, Johnson & Johnson, Labopharm, Lundbeck, Marinus, Neuronetics, Novartis, Noven, Pamlab, Pfizer, Pierre Fabre, Sanofi, Sepracor, Servier, Shire, SK Corporation, Solvay, Somaxon, Tetrigenex, and Vanda; he has served on speaker’s bureaus for Pfizer and Wyeth; and has received grant support from Forest, Johnson & Johnson, Novartis, Organon, Pamlab, Pfizer, Sepracor, Shire, Takeda, Vanda, and Wyeth.

If you would like to comment on this column or submit a suggestion to Dr. Stahl for future columns, please e-mail lla@mbllcommunications.com.

WHICH ANTIDEPRESSANT IS BEST?

If the goal of treatment of depression is sustained remission, it is important to determine which treatment will provide a given patient the best chance of attaining this outcome. Most studies have attempted to answer the question “Which antidepressant is best?” and therefore “Which antidepressant should be first?” by looking at efficacy, side effects, and/or cost. Antidepressants certainly differ in cost and side effects, but there is no consensus as to whether evidence from randomized controlled clinical trials proves that antidepressants differ in therapeutic efficacy, especially in terms of sustaining remission.

Contemporary treatment guidelines for antidepressant use in major depression try to take all three factors of cost, side effects, and efficacy into consideration. The current American Psychiatric Association (APA) treatment guidelines for major depression, now several years out of date, make no recommendation for any specific antidepressant over another, except to state that monoamine oxidase inhibitors (MAOIs) should be used second line.¹ In terms of antidepressant combination or augmentation therapy, the APA guidelines provide little guidance as to which combinations to use, when to use them, or whether to use combination treatment to enhance efficacy or to reduce side effects.

A recent meta-analysis⁵ from the United Kingdom, Europe, and Japan of 12 newer antidepressants from 117 randomized controlled trials of more than 25,000 patients reported that four antidepressants (mirtazapine, escitalopram,

venlafaxine, and sertraline) were more efficacious than some others (duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine), that two of these more efficacious antidepressants (escitalopram and sertraline) also had a better tolerability profile compared to several others (duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine), and that one of these with the best efficacy and tolerability profile had the lowest cost (sertraline), suggesting it might be the best overall choice.

Despite this meta analysis, which has flaws such as not accounting for dosing differences in trials and including non-placebo-controlled studies, as well as many other published and unpublished analyses done by formulary committees in the United States, there is no single “winner” accepted as the best antidepressant to use first. Choice is increasingly being driven by cost, and then among low cost options, by the desire to avoid certain side effects associated with some agents but not with others. Efficacy is not the consideration.

Given the status of the evidence and the huge and potentially high cost demand for antidepressants, the current guidelines as well as actual practice patterns are understandable. When all antidepressants have equal efficacy but differ-

FIGURE 1.
What proportion of major depressive disorders remit?

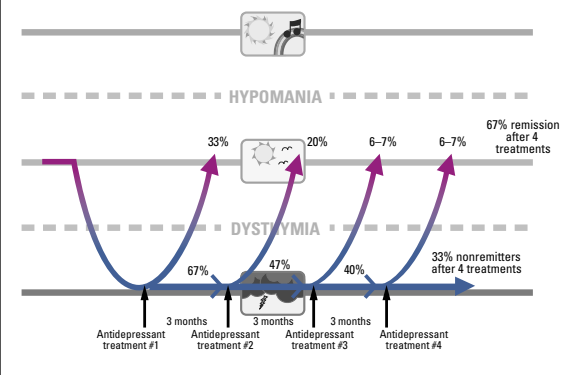
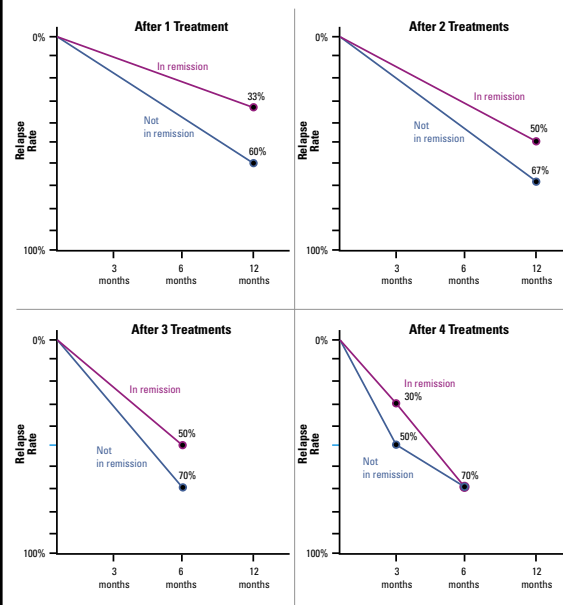


FIGURE 2.
What proportion of major depressive disorders relapse?



ent side effects and costs, the first choice of an antidepressant is driven mostly by cost, especially given the resource consuming observation that 6 antidepressants are prescribed in the US, every second of every minute of every day (IMS Health, personal communication, 2008).

WHICH ANTIDEPRESSANT SHOULD BE NEXT?

Data from US commercial formularies suggest that many patients do not even fill their first prescription for an antidepressant. For those who do, over half do not get a refill of their first antidepressant after a month and only about a quarter get a 3 month's supply or more of their first antidepressant (IMS Health, personal communication, 2008). These data and other similar findings suggest that many patients with depression, perhaps most, are not receiving an adequate trial of their first antidepressant. This may be because they are non-compliant and drop out of treatment, or they are switched to another antidepressant early in treatment. Thus, if the most frequently asked question is "Which antidepressant should be first?" the next most frequently asked question may be "Which antidepressant should be next?"

In practice, the second antidepressant is often selected due to its side effect profile by attempting to give an agent predicted to be more tolerable among the remaining low cost options. For selecting second line antidepressant treatment, efficacy is again not a consideration due to the lack of data suggesting that one agent works better than another after failure of a first treatment.^{3,4} In reality, it is hard to argue against this strategy since comparisons of several specific options after one, two, or three failures of antidepressant treatment choices have shown that all options had the same relative efficacy, but that any treatment given later worked less well than any treatment given early, both in terms of attaining efficacy (Figure 1) and in terms of sustaining efficacy (Figure 2).^{2,4}

IT'S NOT WHICH ANTIDEPRESSANT, BUT WHEN ANTIDEPRESSANT

The results of recent studies suggest that faced with a sequence of choices following unsatisfactory outcomes from a first, second, or third antidepressant treatment, it matters little for remission rates which agent is chosen next or whether one chooses to switch to a second

agent or to continue the first antidepressant and augment with a second therapeutic.^{2,4} What matters seems to be when the agent is given, not which agent is given. Any given antidepressant or combination given late in treatment (after failures of prior antidepressants) appears to work less effectively for attaining and sustaining remission than it will work when given earlier in a sequence of antidepressant treatments.^{3,4} Thus, the real question in selecting antidepressant treatment is now changing to "When should a given antidepressant or combination be given?" and not "Which given antidepressant or combination should be given?"

ARE TWO OR MORE THERAPEUTIC MECHANISMS BETTER THAN ONE?

In a universe where there is great skepticism about whether antidepressants differ in efficacy and all antidepressants appear to have disappointing efficacy in terms of sustaining remission from depression, it is understandable why attention has centered on antidepressant cost and side effects. However, this focus has steered the debate away from the real unmet needs in the treatment of depression: namely, better efficacy defined as higher chances of sustained remission. Only a third of patients attain remission from their first antidepressant and a third of these relapse within a year (Figure 1).^{3,4} Only half of patients are in remission after a year of treatment with 4 consecutive antidepressants of 12 weeks each (Figure 1), and 70% of those who remit after their fourth treatment relapse within 6 months (Figure 2).^{3,4} This is simply not acceptable. While one could continue to focus on cost savings and reducing side effects while hoping that future treatments will improve efficacy when new drugs with novel mechanisms are discovered, it is also possible to develop a strategy now for returning the focus to efficacy, which is urgently needed, by using currently available antidepressant treatments in novel and creative ways.

Specifically, a novel strategy to enhance therapeutic efficacy of antidepressants is emerging by combining multiple simultaneous pharmacologic mechanisms^{6,7} from the initiation of antidepressant treatment⁸ rather than waiting until several treatments fail, and thus to a time when no treatment, including combinations, appears to have a very good chance of working. The rationale for this new multifunctional combina-

tion strategy from the initiation of treatment is threefold:

- (1) Analogy with other areas of medicine;
- (2) Anecdotal clinical observations of antidepressant treatment effects in patients with severe and/or treatment resistant depression; and
- (3) The principle of pharmacologic synergy attained from multiple simultaneous therapeutic mechanisms of action.

Several examples exist from areas of medicine outside of psychiatry about how to enhance therapeutic efficacy of individual agents by combining them, especially at the time when therapy is initiated, not later and after various monotherapies have failed. This includes tuberculosis, HIV infection, and various forms of cancer, among others.⁹ Such a strategy of drug combination from the initiation of treatment has revolutionized the outcomes for these conditions. Whether the biology of depression will be as amenable to a combination approach remains to be determined, but anecdotal clinical observations and preliminary evidence do appear promising.

Most skilled clinicians who treat severe depression and treatment resistant depression with inadequate responses to single agents have seen patients respond to combinations of drugs, as well as to single drugs with combinations of more than one mechanism.^{2,10,11} This includes patients who have poor efficacy after treatment with one or more serotonin selective reuptake inhibitor (SSRI) and who have been switched either to agents with multiple pharmacologic mechanisms such as an serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic antidepressant (TCA), or an MAOI; or augmented with agents having a different pharmacologic mechanism such as bupropion, lithium, thyroid, buspirone, L-methylfolate, hypnotics, anxiolytics, atypical antipsychotics, and others.^{2,10,11} Many of these observations are anecdotal or from uncontrolled studies. Those controlled studies which do exist have failed to clearly show superior efficacy of any dual action agent over any single action agent or superior efficacy of augmentation with a second agent versus switching to another single agent.²⁻⁴

Studies comparing various antidepressant treatment options head-to-head are difficult to do and there are few of them. The lack of positive evidence from controlled trials combining antidepressants does not square with clinical

anecdotes or the standard of care for treatment of severe or resistant cases in clinical practice where the treatment is very individualized and multiple simultaneous pharmacologic mechanisms are routinely prescribed when simpler approaches have failed.^{2,10,11}

One could argue that treatment standards for severe or treatment resistant patients have simply migrated away from the evidence. One could also argue that clinical practice is ahead of and informing clinical trials since there is a growing body of evidence that drug combinations that appear to work in late stage treatment for the most difficult patients when many drugs have failed^{2-4,10,11} may be superior to single agents for sustained remission of depression when given early in treatment.⁸

Thus, the current question is not only whether multiple mechanisms are better than single mechanisms, but also whether giving the same multifunctional treatments that may work anecdotally after several treatments have failed in some severe and treatment resistant cases will also enhance the remission rates and sustain them for longer periods of times in first line patients.⁸ That is the focus of many current and ongoing investigations, many of which are reviewed here.

Finally, it is a general principle of pharmacology that some mechanisms can add independently to the actions of others; and that some sets of mechanisms can even provide "supra-additive" or synergistic actions when added together.⁹ This certainly seems to be the case for tuberculosis and HIV. For psychopharmacology, it is an active theory that multiple simultaneous pharmacologic mechanisms may be superior in terms of efficacy for depression,^{2,6,7} but it is not yet clear whether enhancing the neurotransmission of two or three monoamines (ie, serotonin [5-HT], norepinephrine [NE], and dopamine [DA]) rather than just one provides more efficacy for depression or whether acting at one monoamine neurotransmitter plus a different neurotransmitter system such as γ -amino butyric acid (GABA) and glutamate can provide the therapeutic synergies we are seeking for sustaining remission in depression and thus improve outcomes. However, it is clear that the therapeutic agents with such mechanisms are available to test in combination in order to address the question of whether two or more mechanisms are better than one.

GIVE THE BEST TREATMENT FIRST OR SAVE THE BEST FOR LAST?

If antidepressant combinations have some precedent for working in the most difficult cases when single agents fail, the question then turns to "Should the best treatment be given first or shall we continue to save the best for last?"

Evidence is now accumulating that starting combination therapy from the very initiation of treatment for major depression may enhance outcomes, attaining higher remission rates and lower relapse rates than with single antidepressants.⁸ Starting rather than ending with a multifunctional pharmacologic approach by utilizing more than one therapeutic agent would represent a major paradigm shift in the treatment of depression. Combining two therapeutic agents from the very initiation of treatment may lead to enhanced outcomes compared to treatment with a single antidepressant but would be going against the grain for current practices of how to choose antidepressants. The combination approach would likely be somewhat more expensive and in some cases cause more side effects, depending upon the specific combinations chosen. Thus, many questions remain to be answered. The value of this combination approach from the initiation of treatment will be whether it enhances efficacy for sustained remission. If so, the implementation of this approach into widespread clinical practice will be determined by whether any such benefits of efficacy are worth the possibility of increased costs and side effects.

ANTIDEPRESSANT AUGMENTATION WITH NATURAL PRODUCTS

Natural products have long enjoyed popular appeal for use as adjunctive treatments for depression.¹² However, commercial barriers have caused most of the evidence for use of natural products to come from small, often single center academic investigations and not from large industry funded and US Food and Drug Administration registration caliber studies. Nevertheless, preliminary if inconsistent evidence for the antidepressant efficacy, alone or in combination with antidepressants, for some natural products such as folate, L-methylfolate, S-adenosyl-methionine (SAME), omega 3 fatty acids, St. John's wort, and others does exist.¹² This includes specific evidence that combination of folate/L-methylfolate with antidepressants from the initiation of treatment enhances antidepressant efficacy.⁸

One potential advantage of augmenting a traditional antidepressant with a natural product is that natural products have low liability for side effects and those that do occur are usually easily distinguishable from the side effects of traditional antidepressants.¹² This aspect could potentially remove one of the biggest barriers to giving antidepressant combination therapy, namely the wish to avoid the simultaneous onset of side effects from two different antidepressants.

Natural products are generally less expensive than name brand antidepressants. Patients are often more willing to pay out of pocket for natural products than for traditional antidepressants. The costs of natural products are often not covered by commercial formularies, thus reducing overall costs compared to augmenting with two branded antidepressant treatments, at least from a commercial payor perspective. Thus, natural products may have some potential side effect and cost advantages compared to other combination strategies; the real question is how to maximize efficacy with natural products.

ANTIDEPRESSANT COMBINATION WITH FOLATE/L-METHYLFOLATE: THEORETICAL MULTIFUNCTIONAL MECHANISM

One of the first agents conceptualized to be a combination therapy from the initiation of treatment of major depression is synthetic folic acid and its centrally active natural derivate L-methylfolate. Beyond just a general sense of "natural products encourage wellness," what might be the specific multifunctional pharmacologic rationale for a combination of an SSRI with L-methylfolate?

Consequences of low folate/L-methylfolate

A number of empiric observations link folate/L-methylfolate with depression and with antidepressant action.¹³ Folate deficiency has long been associated with depression, and with later onset of action, lesser improvement, a more severe depressive episode, and higher chances of relapse when taking an antidepressant.¹³ Treatments with folic acid, L-methylfolate, and folinic acid have all been associated with antidepressant effects or the enhancement of the therapeutic benefits of lithium.¹³ Dietary intake of dihydrofolate, foods fortified with folic acid, or vitamins containing folic acid are all converted to the centrally active agent

L-methylfolate by the enzyme methylene tetrahydrofolate reductase (MTHFR).¹³ A specific variant of this enzyme (C677T) reduces the formation and functional availability of L-methylfolate, raises the levels of homocysteine, and increases the incidence of depression.¹⁴⁻¹⁸

The monoamine hypothesis of depression links major depression to a deficiency of one or more of the monoamines 5-HT, DA, and NE, and antidepressant actions to the boosting of one or more of these monoamines.² L-methylfolate regulates the synthesis of the bipterin cofactor used by the rate limiting enzymes tyrosine hydroxylase and tryptophan hydroxylase that synthesize the three monoamine neurotransmitters from amino acid precursors (Figure 3).^{2,13,19} Deficiency of bipterin reduces monoamine levels, so L-methylfolate can be considered a "trimonoamine modulator" by regulating the levels of bipterin available for monoamine synthesis (Figure 3).^{2,13,19}

Possible pharmacological mechanism of L-methylfolate in boosting antidepressant action

These various observations suggest a mechanism by which L-methylfolate could enhance

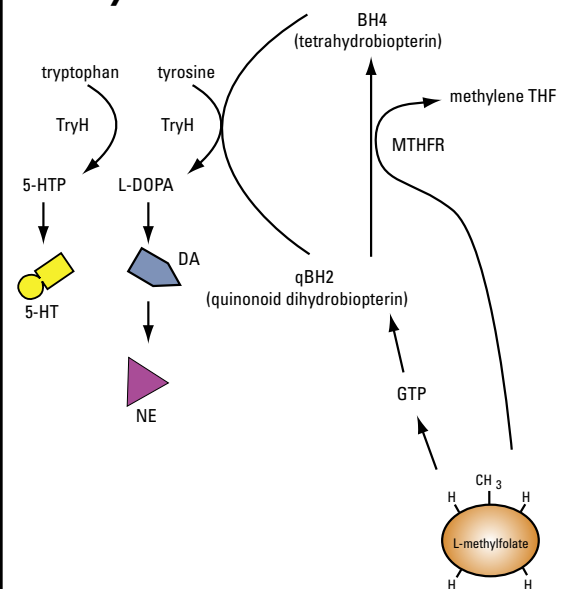
the efficacy of antidepressants.^{2,13} If low folate/L-methylfolate levels lead to diminished availability of monoamine neurotransmitters, this could in turn lead to depression in some patients (Figure 4A). Diminished availability of monoamines may compromise the ability of antidepressants to work (Figure 4B), since all known antidepressants work indirectly via enhancing the availability of the monoamines.²⁰ Without 5-HT available for synaptic release, a reuptake inhibitor would theoretically be ineffective (Figure 4B). However, repletion of L-methylfolate levels would theoretically boost monoamine synthesis (Figure 4C) and this would potentially boost the efficacy of antidepressants (Figure 4D).^{2,13,19}

BEST CANDIDATES FOR FOLATE/ L-METHYLFOLATE COMBINATION

Low folate/high homocysteine levels

The question arises as to whether the SSRI/L-methylfolate combination strategy makes sense for all patients from the initiation of antidepressant therapy or whether a particularly vulnerable subpopulation could be identified where efficacy may be greater. One possibility is to

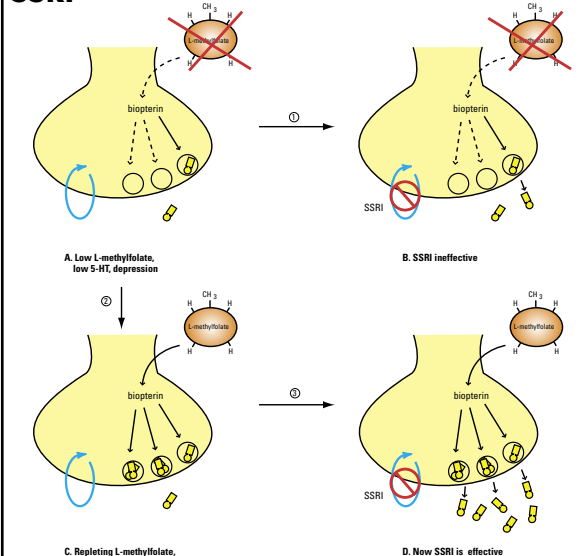
FIGURE 3. Regulation of monoamine synthesis by L-methylfolate



THF=tetrahydrofolate; MTHF=methylene tetrahydrofolate reductase; L-DOPA=levodopa; 5-HT=serotonin; DA=dopamine; NE=norepinephrine; GTP=guanosine triphosphate.

Stahl SM. *CNS Spectr.* Vol 15, No 2. 2010.

FIGURE 4. How L-methylfolate could enhance the antidepressant effectiveness of an SSRI



SSRI=selective serotonin reuptake inhibitors; 5-HT=serotonin.

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focus on patients with certain high risk factors, such as those with documented low folate levels or at high risk for having low folate levels, including certain drugs, disease states, and high risk genotypes. For example, those with documented low folate levels might be the best candidates for this approach given the postulated mechanism of L-methylfolate when combined with antidepressants (Figure 4).^{13,20} In fact, those who responded in the combination from the initiation of therapy trials were those whose folate levels went up with folate/L-methylfolate treatment, although some patients who responded did not necessarily have low baseline serum folate levels prior to treatment.^{13,21-23}

What needs to be determined now is whether measuring serum folate levels (indicative only of recent folate ingestion), red blood cell (RBC) folate levels (indicative of longer term folate levels), or even serum homocysteine levels which vary inversely with folate levels, might identify the best candidates for L-methylfolate augmentation. Also, it would be useful to know if those whose serum or RBC folate levels rise, or homocysteine levels fall after L-methylfolate treatment, are the best candidates for long term L-methylfolate augmentation.

Determining folate levels would certainly be useful in patients who are found to have low serum folate; however, serum folate levels may not accurately reflect central nervous system (CNS) L-methylfolate levels. Also, when "serum folate" levels are determined, this is usually a measure of all forms of folate (synthetic folic acid, tetrahydrofolate, methylene THF, L-methylfolate, etc.) without a specific measurement of the CNS active form, L-methylfolate.

In addition, these laboratory tests add to the cost of treatment, so one might opt for clinical screening procedures to identify those depressed patients that have high risk factors for low folate/high homocysteine levels, such as smoking, alcoholism, poor nutrition, gastrointestinal and absorption disorders including bulimia and anorexia nervosa, pregnancy, medications that may interfere with folate absorption or conversion into L-methylfolate such as anticonvulsants, oral contraceptives, metformin, lithium, dopamine agonists, and others.^{13,24}

Pharmacogenomics and Epigenetics

There may be other types of functional folate deficiencies that are more subtle than just serum

or RBC levels of folate or homocysteine. For example, the T genotype of the MTHFR enzyme reduces MTHFR activity, decreases L-methylfolate levels, and increases plasma homocysteine levels.¹⁴⁻¹⁸ The odds of having two copies of the T form of this enzyme are reported to be greater in Hispanic and Mediterranean populations, and are reported to be almost three times greater in depressed patients as in the normal population.¹⁴⁻¹⁸ If this test is too expensive for routine use, an alternative is to consider the use of the L-methylfolate combination strategy from the initiation of antidepressant treatment especially in higher risk depressed patients of Hispanic or Mediterranean background.

Ultimately, genotyping and epigenetic markers will come into psychiatry, and when they do, they are anticipated to be useful in identifying patients more likely to respond to one treatment versus another.^{25,26} Currently, these are only research tools but one can anticipate the possibility that this approach could soon identify high risk groups that would theoretically respond best to a specific augmentation/combo strategy. It is already possible to foresee a possible high risk group that might benefit most from L-methylfolate augmentation, but this will require much further investigation.

Two other risk factors, one genetic and one epigenetic, are also theoretically linked to the possibility of reduced functional activity of L-methylfolate and to symptoms of depression that might benefit especially from the L-methylfolate augmentation strategy. They are the val genotype of the DA metabolizing enzyme Catechol-O-methyl transferase (COMT),^{2,14,27-38} and the epigenetic risk factor of reduced histone and DNA promoter methylation for the COMT gene.^{26,39-43}

Individuals with the val genotype of this enzyme have higher COMT activity and consequently lower DA levels in prefrontal cortex, a condition that reduces the efficiency of processing of cognitive information, potentially increasing the risk of cognitive symptoms in depression.^{2,14,27-38} The activity of COMT is further regulated by a gene promoter that determines the number of copies of this enzyme that are made.^{2,26,39-43} In situations where methylation of this promoter is low, such as can occur when levels of the critical methyl donor L-methylfolate are low, extra copies of this enzyme are made, further lowering DA levels in prefrontal cortex, possibly increasing the risk for cognitive symptoms.

In reality, deciding which treatment might fit any given patient will likely become linked to the convergence of risk factors.^{25,26} One hypothetical scenario for the type of depressed patient who may be particularly well matched to L-methylfolate augmentation could be the “triple whammy” case where the T genotype of MTHFR (with consequent low levels of L-methylfolate and possible low levels of monoamines) is matched with low methylation of the COMT gene, in patients who specifically express the val genotype for this enzyme, leading to increased metabolism of already low DA levels by COMT with high activity and extra amounts expressed.

Whether this type of strategy will eventually identify the candidates for the various available treatment strategies in depression remains to be determined by future research. But matching the correct strategy to the correct patient is more likely to enhance the efficacy of the treatments currently available more than a “one treatment fits all” approach.^{25,26,39} Until then, perhaps a prudent weighing of the available risk factors for any given patient can help a clinician determine which specific treatment option to select. Currently, this is more of an art than a science.

ANTIDEPRESSANT COMBINATION WITH FOLATE/L-METHYLFOLATE FROM THE INITIATION OF TREATMENT: CLINICAL DATA

Three randomized controlled trials have shown superior efficacy of antidepressant-folate/methylfolate combinations from initiation of therapy compared to antidepressants alone.²¹⁻²³

In the first study, depressed patients specifically with low RBC folate levels were given treatment as usual in the pre-SSRI era and randomized to either 15 mg/day racemic methylfolate or placebo from the initiation of therapy. Serum and RBC folate levels increased, and clinical measures of mood improved significantly in the antidepressant/methylfolate group compared to the antidepressant monotherapy group.²¹

A second study randomized patients with major depression to the SSRI fluoxetine plus 0.5 mg of folate or to fluoxetine alone.²² Not surprisingly, plasma folate levels rose in the folate treated group, especially in women, but plasma homocysteine levels (which L-methylfolate converts into methionine and then SAME)¹³

declined only in women. Patients on fluoxetine/folate had significant improvement in depression than patients on fluoxetine alone, but this was accounted for entirely by the women who improved. The authors suggested that folate be dosed sufficiently to show a physiological effect, namely lowering of homocysteine levels in order to optimize potential antidepressant actions. As 0.5 mg of folate is a much lower dose than the equivalent dosing of the first study, this 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 investigated fluoxetine plus either 10 mg of folate or fluoxetine plus placebo.²³ Homocysteine levels were documented to decrease in the patients receiving folate and they also had significantly lower depression scores compared to 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, with measurement of folate and homocysteine levels, is ongoing (ClinicalTrials.gov NCT00321152 and NCT00955955: A study of 6(S)-5-MTHF among SSRI-resistant outpatients with major depressive disorder). If this study confirms the others, it may provide clearer guidelines on potential dosing of the centrally active L-methylfolate in antidepressant treatment combination from the start.

ANTIDEPRESSANTS PLUS HYPNOTICS FROM THE INITIATION OF TREATMENT

Hypnotics have long been the most common augmenting agents prescribed concomitantly with antidepressants, and indeed, many antidepressants are also hypnotics. Insomnia is not only a prominent symptom of depression in most patients, but it is the most common residual symptom preventing full remission after treatment with an antidepressant.^{2,44} No wonder that antidepressants with sedative properties are often chosen for patients with insomnia or that hypnotics have been so commonly added to antidepressants.

Although many clinicians prescribe a sedating antidepressant to achieve both hypnotic and antidepressant actions in a single drug, most cli-

icians will wait to add a hypnotic to an antidepressant until the antidepressant has been given for a few weeks and only if insomnia persists. This approach is often taken because insomnia as a symptom of depression will often respond as the depression gets better without addition of a hypnotic. It can be easier to manage tolerability issues when one drug is added at a time rather than giving two drugs at once, increasing the chances of side effects and making it more difficult to attribute any emergent side effects to one drug or the other.

Recent developments are now challenging the wisdom of waiting to augment antidepressants with hypnotics. Firstly, the Sequenced Treatment Alternatives to Relieve Depression study suggests that the chances of attaining sustained remission after any given treatment are reduced if prior treatments have been given and have failed to attain remission,^{3,4} often because of residual insomnia.^{2,44} Secondly, enhanced efficacy for remission of depression is being increasingly reported for antidepressants that themselves have hypnotic effects. This may be due to the possibility that giving some antidepressant monotherapies is the same as giving a standard antidepressant plus a standard hypnotic in a single molecule.

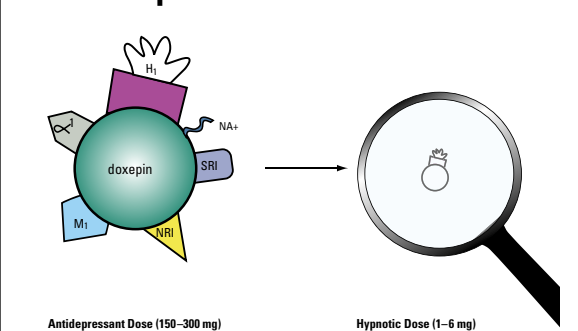
Agents with multifunctional antidepressant plus hypnotic actions include the H₁ antagonist TCAs such as doxepin⁴⁵; some H₁ antagonist atypical antipsychotics such as quetiapine²; the 5-HT_{2A} antagonists trazodone and all atypical

antipsychotics^{2,46}; and the melatonergic actions of the novel and newly approved (outside the US) antidepressant agomelatine.⁴⁷ Very low doses (<10 mg) of doxepin (enough for hypnotic effects, too low a dose for antidepressant effects) (Figure 5) and other TCAs may thus be useful augmenting agents for insomnia when added to an antidepressant for some patients.⁴⁵

Very low doses of quetiapine (“baby bear” doses in Figure 6) are already often used to augment antidepressants in order to treat insomnia associated with depression. This is currently an expensive option that is also associated with metabolic side effects. On the other hand, moderate doses of quetiapine (“mama bear” in Figure 6) have very robust effect sizes in the treatment of bipolar depression, and not just insomnia, with moderate dose mechanisms linked both to monoamine enhancing actions of the active metabolite norquetiapine (on 5-HT_{2C}, 5-HT_{1A} receptors and norepinephrine transporters) and to hypnotic actions of H₁ histamine antagonism.²

These multifunctional pharmacologic properties of quetiapine and its active metabolite norquetiapine may explain why quetiapine is often effective as a monotherapy, given that as a single molecule it is already a combination of mechanisms (see Figure 6 for the hypnotic mechanism at low doses with H₁ antagonism of “baby bear;” for antidepressant mechanisms at moderate doses with 5-HT_{2C} antagonism, 5-HT_{1A} partial agonism, and NE transporter blockade of “mama bear;” and for the antipsychotic

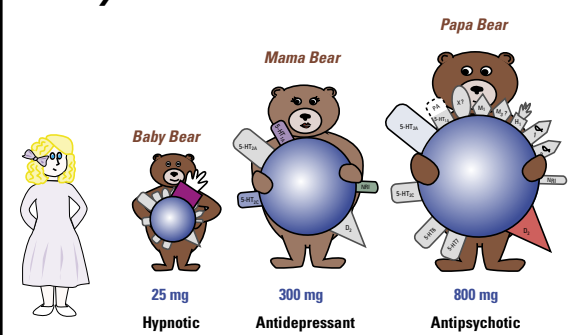
FIGURE 5.
High antidepressant versus low hypnotic doses of the tricyclic antidepressant doxepin



H=histamine; SRI=serotonin reuptake inhibitor; NRI=norepinephrine reuptake inhibitor; M=melatonin.

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FIGURE 6.
Quetiapine and multifunctional actions: A story of three bears and three doses



5-HT=serotonin; D=dopamine; H=histamine; M=melatonin; NRI=norepinephrine reuptake inhibitor.

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mechanism of high doses with D₂ antagonism of “papa bear”).²

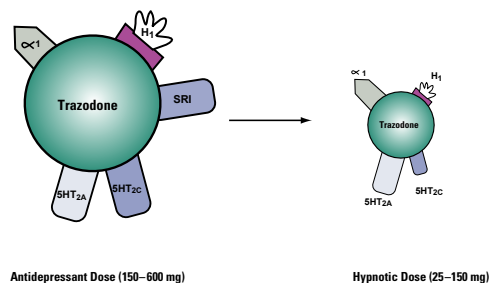
Trazodone is actually the most commonly prescribed hypnotic, especially in psychiatry as an augmenting agent to antidepressants.² Due to its short half life and sedating side effects, trazodone is generally given once a day at night and in a dose too low to work as an antidepressant, but adequate to work as a hypnotic even as a monotherapy.⁴⁶ When added to an SSRI/SNRI, the potent 5-HT_{2A} antagonist properties of low dose trazodone (Figure 7) could theoretically exert synergistic antidepressant actions due to effects on enhancing monoamines.^{2,46} Indeed, raising the dose of trazodone (Figure 8) itself may accomplish this by recruiting additional multifunctional mechanisms of 5-HT reuptake blockade and 5-HT_{2C} antagonism to 5-HT_{2A} antagonism (Figure 8), but this can be too sedating during the day. The pending availability of a controlled release version of trazodone may reduce its sedative properties at high antidepressant doses and allow higher than currently prescribed low hypnotic doses of trazodone to be given either as monotherapy or as augmentation therapy with the theoretical potential to further boost antidepressant efficacy.⁴⁶

A third reason to augment an antidepressant with a hypnotic is due to the results emerging from a set of studies augmenting antidepressants with eszopiclone, a GABA_A positive allosteric modulator (a “Z” drug).² Combining eszopiclone with the SSRI fluoxetine from the initiation of treatment in depressed patients with insomnia, compared to treatment with fluoxetine alone resulted in remarkable improvement not just in the symptom of insomnia, but in other symptoms of depression, including an enhanced remission rate (Figure 9).

This surprising set of results has come from the innovative study of Fava and colleagues.⁴⁸ 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 (Figure 9). 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 plus either eszopiclone or placebo.⁴⁹ 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, since eszopiclone has specific actions on GABA_A receptor isoforms that differ from the actions of other Z drugs.⁵⁰ That may explain why the results with

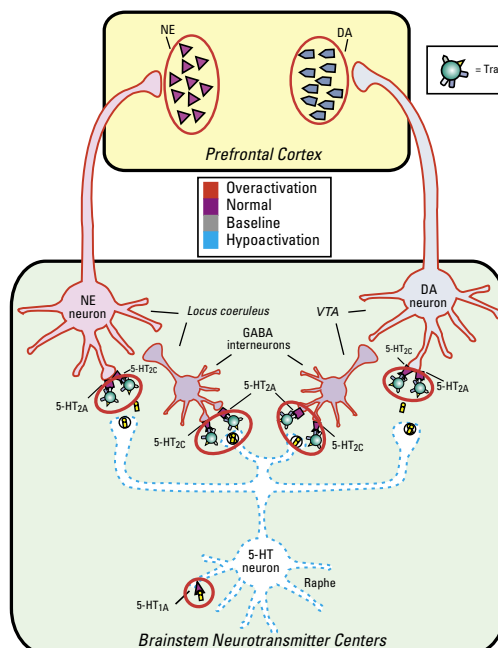
FIGURE 7.
High antidepressant versus low hypnotic doses of trazodone



H=histamine; SRI=serotonin reuptake inhibitor; 5-HT=serotonin.

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FIGURE 8.
Mechanism of antidepressant action of trazodone: Serotonin stimulation of 5-HT_{1A} receptors potentiates the NE and DA disinhibition of 5-HT_{2A} and 5-HT_{2C} antagonism



NE=norepinephrine; DA=dopamine; 5-HT=serotonin.

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eszopiclone were not replicated by the same group using another Z drug, zolpidem.⁵¹

It is of great interest to determine which sleep enhancing effects of the many different hypnotic mechanisms could have the potential to enhance antidepressant efficacy when added to antidepressants, whether via two different drugs or via a single drug with multifunctional pharmacologic properties. Hypnotic mechanisms range from Z drugs, to 5-HT_{2A/2C} antagonists,^{2,46} to melatonin (M)₁ and M₂ agonism (such as via the selective agent, ramelteon or via the multifunctional agent with melatonergic and 5-HT_{2C} antagonist properties, agomelatine),^{2,47} to atypical antipsychotics with potent antihistamine properties (such as quetiapine and its active metabolite norquetiapine).² The data suggest that improving insomnia does more than enhance sleep related symptoms. It may also enhance remission from depression and the chances of this may be enhanced the earlier this is done in the treatment algorithm.

Various hypotheses exist to explain this positive action of hypnotics on remission from depression, from the possibility that sleep is inherently “curative” for depression to the idea that insomnia as a residual symptom of depression creates an allostatic mechanism for pulling the brain back into a full blown episode of depression if insomnia is allowed to persist.²

Further replication of this work of combining hypnotics with antidepressants from the initiation of treatment must be done. In the mean-

time, these findings do encourage the use of multifunctional monotherapies that are themselves both antidepressants and hypnotics for depressed patients with insomnia. It also suggests that hypnotics, if not given simultaneously with antidepressants, might be given very soon after the initiation of an antidepressant, perhaps within days rather than within weeks of starting an antidepressant, to boost the chances of sustained remission.

This approach of combining a hypnotic with an antidepressant from the initiation of treatment may not be for all depressed patients, as it certainly makes more sense in patients with insomnia than for those with hypersomnia or who experience daytime fatigue and slowed concentration, especially if such symptoms are worsened by a hypnotic or sedating antidepressant. Whether other ways to identify the best patients for the combination of hypnotics with antidepressants will emerge from clinical profiling or from pharmacogenomics remains to be determined.

ANTIDEPRESSANTS PLUS ANTIDEPRESSANTS

Combining antidepressants with antidepressants is increasingly the approach to end stage treatments of depression, when all else has failed.^{2,11} The idea of combining two antidepressants for such difficult cases is to combine multiple independent pharmacologic actions on one, two, or three of the monoamines in the hopes that this will generate more antidepressant efficacy (Figure 10). Increasingly, the use of

FIGURE 9.
Enhanced remission of depression and GAD when the hypnotic eszopiclone is added to an SSRI

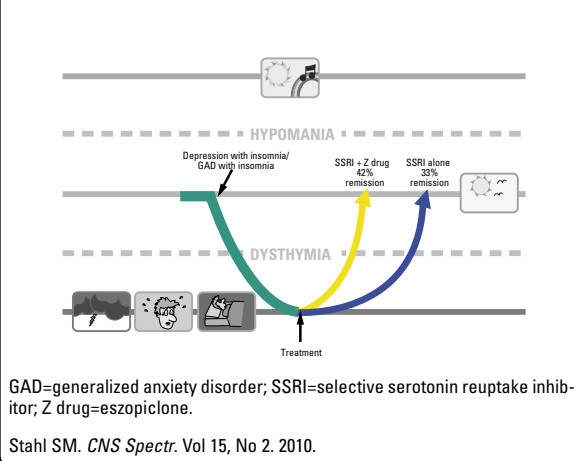
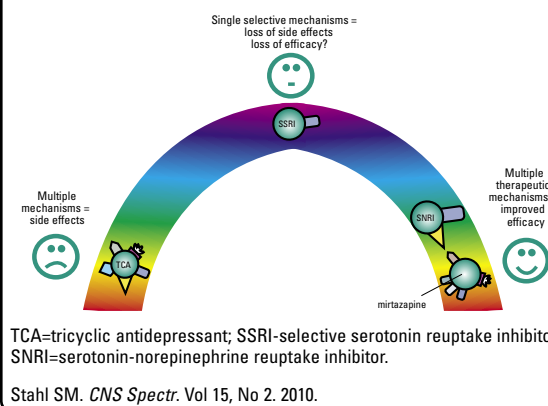


FIGURE 10.
Are two antidepressant mechanisms better than one?



antidepressant combinations is moving up to second line treatment after the first treatment with a monotherapy has failed to attain remission. However, antidepressant combination at this point in treatment is often only done if the patient tolerates a monotherapy and also has some reasonable, if incomplete, response to it. In that case, the monotherapy is continued and a second antidepressant is added.^{2,11} If a patient does not tolerate a monotherapy or has no therapeutic effects at all, that patient is more likely to be switched to another monotherapy than to continue an inactive or intolerable monotherapy augmented with another.

An increasing number of studies combining two antidepressants from the initiation of treatment are being conducted and published. This is not surprising since many of the newest and most effective monotherapies are actually themselves multifunctional drugs: SNRIs with both serotonergic and noradrenergic (and cortical dopaminergic) actions; norepinephrine dopamine reuptake inhibitor bupropion (NDRIs) with both noradrenergic and dopaminergic actions; and mirtazapine with α_2 antagonism, and 5-HT_{2C} antagonism plus 5-HT_{2A} antagonism plus H₁ antagonism, which appears to have triple actions on disinhibiting NE, DA, and 5-HT release; and, of course, atypical antipsychotics with complex pharmacologic actions and emerging antidepressant actions.²

Combining two agents, especially a simpler SSRI with one of these multifunctional agents, allows more flexibility in combining multiple pharmacological mechanisms with the strategy that this will lead to therapeutic synergy for sustained remission in depression. However, many of these agents with multiple mechanisms have considerable side effects on their own, let alone when combined with another drug.

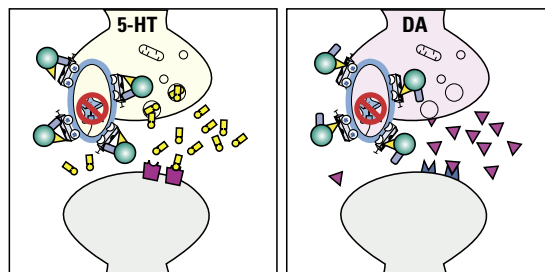
This problem of enhancing side effects while enhancing efficacy also exists when multiple agents are added together at the initiation of treatment for tuberculosis, HIV infection, and cancer chemotherapy, but are justified in these conditions because of the enhanced efficacy gained there. To the extent that combinations of antidepressants are proven to result in enhanced efficacy for sustained remission from depression, combinations of antidepressants from the initiation of treatment will also be justified. Recent and ongoing studies of antidepressant combinations from the initia-

tion of treatment are indeed encouraging in this regard.

For example, Nelson and colleagues⁵² showed that the combination of the SSRI 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.⁵² This is very much like turning a serotonin selective agent plus a noradrenergic agent into an SNRI strategy (Figure 11).² In fact, the most common augmentation strategy other than trazodone to add to an antidepressant is the NDRI bupropion (Figure 12), which not only produces the same pharmacology as an SNRI (Figure 11) when added to an SSRI, but also additional pro-dopaminergic actions in the prefrontal cortex (Figure 13).²

Blier and colleagues^{53,54} are also conducting a series of very novel studies of antidepressant combinations with mirtazapine (Figure 14),

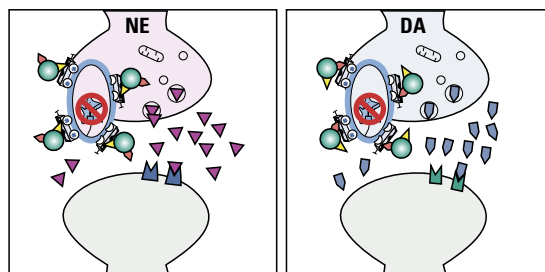
FIGURE 11.
SNRI action



SNRI=serotonin-norepinephrine reuptake inhibitor; 5-HT=serotonin; DA=dopamine.

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FIGURE 12.
NDRI action



NDRI=norepinephrine-dopamine reuptake inhibitor; NE=norepinephrine; DA=dopamine.

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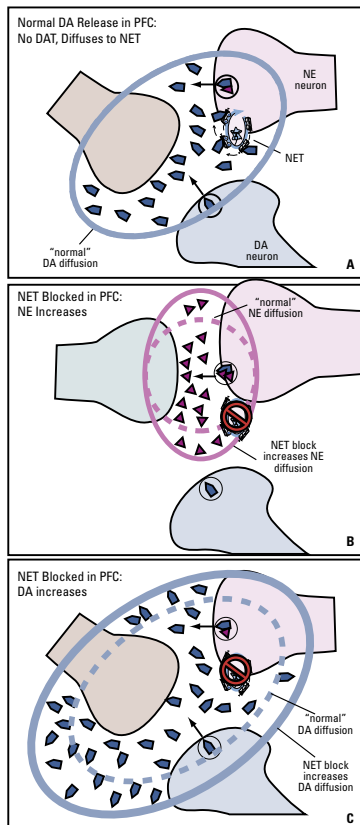
showing in one study that remission rates on the SSRI paroxetine plus mirtazapine were double the rates on the single drugs.⁵³ Further studies by this group suggest that remission rates on several combinations of antidepressants also roughly doubled the remission rates on a single agent (specifically, mirtazapine plus either fluoxetine, venlafaxine, or bupropion vs. fluoxetine alone).⁵⁴ In each of these cases, a monoamine reuptake inhibitor for 5-HT, NE, and/or DA is combined with a monoamine disinhibitor for these same monoamines (ie, mirtazapine) (Figure 14) that acts by a different mechanism than reuptake blockade, namely by α 2A antagonism (Figure 15) and by 5-HT_{2C} antagonism (Figure 16).² This leads to synergistic increases in the monoamine levels, and perhaps not surprisingly, to apparent evidence of synergistic

actions in the treatment of depression.

Often such combinations are used only late in the treatment algorithm when heroic approaches seem justified, as in the designation "California rocket fuel" to try to blast someone out of a deep depression (Figure 17).² The possibility that by giving these same combinations from the initiation of treatment could result in better sustained remission rates than with monotherapies is indeed quite provocative. It is encouraging that additional anecdotal and retrospective observations are now emerging to support this possibility.⁵⁵

These very promising findings of Blier's

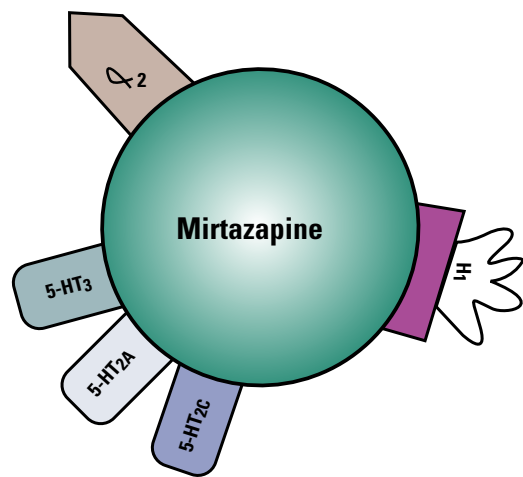
FIGURE 13.
Effects of NET Blockade on NE and DA Levels in PFC



NET=norepinephrine transporter; NE=norepinephrine; DA=dopamine; PFC=prefrontal cortex.

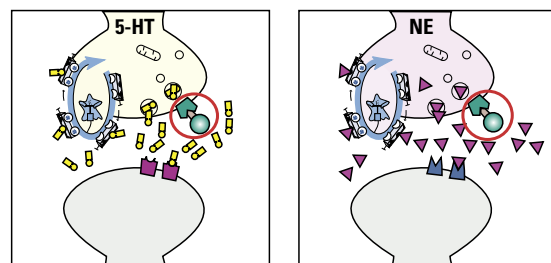
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FIGURE 14.
Pharmacologic properties of mirtazapine



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FIGURE 15.
Mechanism of mirtazapine as an α 2 antagonist and 5-HT and NE disinhibitor



5-HT=serotonin; NE=norepinephrine.

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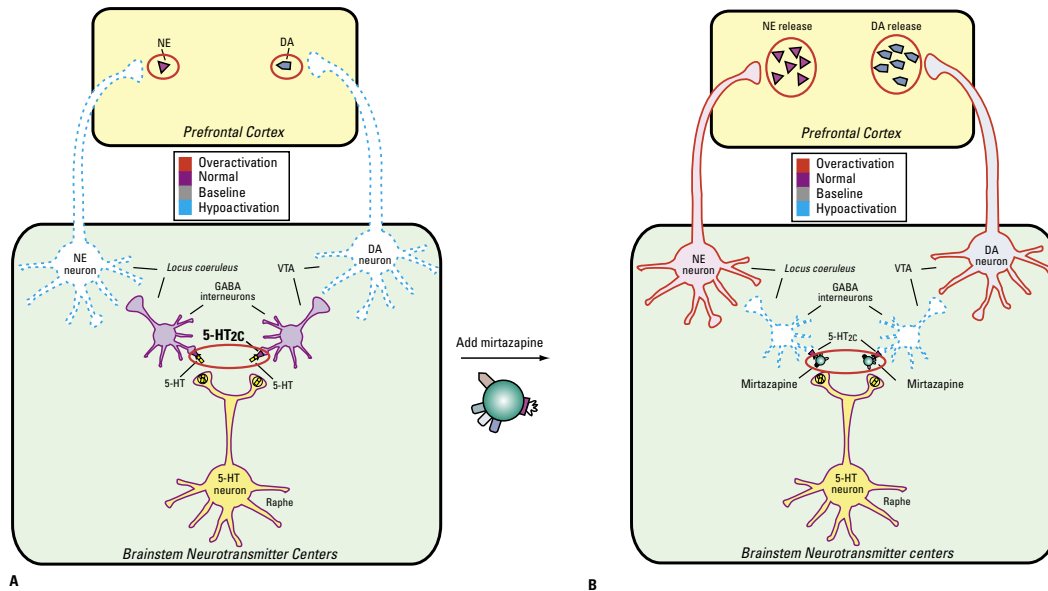
group are now being followed up by a major study funded by the National Institute of Mental Health (Combining Oral Medications to End Depression Study) comparing the potential benefits of adding any two of the agents bupropion, escitalopram, mirtazapine, or venlafaxine from treatment initiation. If these results replicate the doubling of remission rates seen in previous studies, there will likely be a rapid shift to using

two agents from initiation of treatment for a major depressive episode.

OTHER POSSIBLE COMBINATIONS

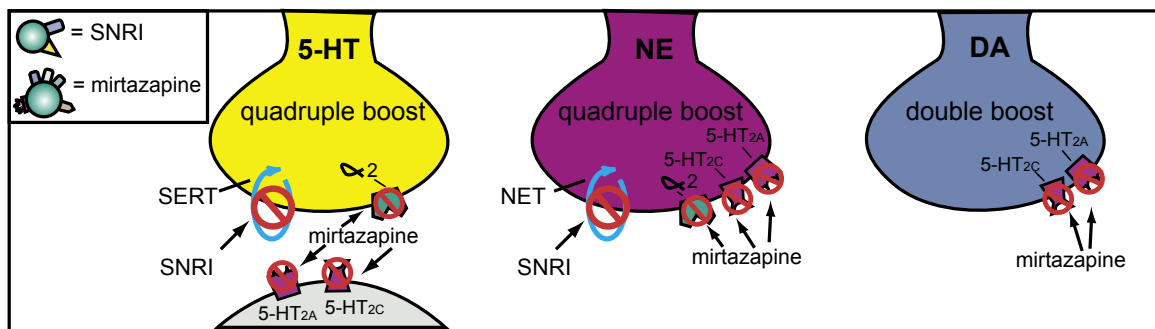
Lithium, buspirone, thyroid, atypical anti-psychotics, lamotrigine, dopamine agonists, modafinil, stimulants, and other agents could all potentially be added to antidepressants from

FIGURE 16. Mechanism of Mirtazapine as a 5-HT_{2C} Antagonist and Norepinephrine and Dopamine Disinhibitor in Prefrontal Cortex



NE=norepinephrine; DA=dopamine.
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FIGURE 17. California rocket fuel: SNRI + mirtazapine



SNRI=serotonin-norepinephrine reuptake inhibitor; 5-HT=serotonin; NE=norepinephrine; DA=dopamine; SERT=serotonin transporter; NET=norepinephrine transporter.

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the initiation of treatment,^{2,11} but have largely not been studied. The cost and side effects of atypical antidepressants will likely create considerable resistance to using them first line, as will the use of highly scheduled substances such as stimulants. On the other hand, lithium, buspirone and thyroid have long been used in combination later in treatment,²⁻⁴ so it would be useful to see investigations of their use from the initiation of treatment, as would studies of lamotrigine and dopamine agonists in selected cases.

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. **CNS**

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