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MOOD DISORDERS (SM STRAKOWSKI, SECTION EDITOR)

Antidepressant Combinations: Cutting Edge Psychopharmacology or Passing Fad?

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Abstract This article reviews the rationale for and history of combining antidepressants, as well as the current state of the evidence, in the treatment of major depression. Although it has long been suggested that some individuals may benefit from regimens that combine two dissimilar antidepressants, enthusiasm for this practice has waxed and waned and there was never a strong empirical foundation to support this practice. The tangibly better safety profiles of the newer generation antidepressants, both singly and in combination, have permitted greater use of such combinations in contemporary practice than ever before. Combinations that pair a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) with a dissimilar antidepressant, such as bupropion or mirtazapine, are now widely used for patients who have not responded to trials of first- or second-line antidepressant monotherapies and have been tested as a potential way of speeding the benefits of treatment. However, there still is no strong evidence that even the most widely used combinations have particular merit and clinicians should be mindful that alternatives exist with more established efficacy. Moreover, aside from selected cases of drug-drug interactions, it may take full therapeutic doses of both drugs across a typically adequate duration of exposure to achieve the desired effects of combined treatment.

Keywords Antidepressants · Selective serotonin reuptake inhibitor · SSRI · Serotonin norepinephrine reuptake inhibitor · SNRI · Tricyclic antidepressant · TCA · Monoamine oxidase inhibitor · MOI · Bupropion · Mirtazapine · Psychopharmacology · Mood disorders · Psychiatry

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Introduction

There is no doubt in the management of depressive disorders that psychiatrists are routinely combining antidepressants in contemporary practice [1•] and the scope of this practice has now expanded to include management of difficult-to-treat depressive disorders, targeted treatment of specific residual symptoms or side effects, and attempts to accelerate the benefits of treatment in order to improve outcomes by reducing side effects or relieving persistent residual symptoms [2•, 3]. Antidepressant combinations thus appear to play an important role in the contemporary management of major depressive disorder (MDD). One might view this practice as an example of crafting a "multi-modal" therapy [2•] or "rational" co-prescription [4], in which the oppressive shackles of conventional orthodoxy have been removed, and creative clinicians are now able to mix and match various treatment combinations as was never before possible. As appealing as this view of the state of the art sounds, however, clinicians must recognize that simply because two treatments can usually be safely combined does not mean that they have additive or synergistic effects and that the practice of combining antidepressants is not well-anchored by empirical data [5]. As such, there remain legitimate doubts about whether this strategy is a truly valuable way to improve patients' outcomes or whether the "art" of combining antidepressants is better understood as a fad that has been necessitated by the limits of our current state of therapeutics, which will eventually be replaced by other, more promising strategies.

This paper briefly reviews the rationale for combining antidepressants and summarizes the evidence for and against the use of combined antidepressant regimens. It is concluded that the more commonly used antidepressant combinations are generally safe and that, at the least, the practice of combining antidepressants can be an expeditious way to minimize the incidence of discontinuation symptoms or decrease time lost

to cross-titration or drug wash-outs. There remains, however, little reason to believe that these strategies are highly or uniquely effective, especially when compared to better proven strategies, such as monotherapy with third- or fourth-line antidepressants (i.e., tricyclic antidepressants [TCAs] or monoamine oxidase inhibitors [MAOIs]) or the several empirically validated adjunctive strategies (e.g., augmentation of the antidepressant with lithium or a second generation antipsychotic medication such as aripiprazole or quetiapine).

Rational Co-Prescription or Polypharmacy?

Was Shakespeare serious when he had Juliette assert that "…a rose By any other name would smell as sweet"? With respect to perception of the risks and benefits of a medical practice, the name used to describe that practice can make a big difference! In this case at hand, the term Polypharmacy can be used to describe the simultaneous prescription of two antidepressants and this name conjures up a much different set of images than terms such as "rational co-prescription" or "multi-modal antidepressant therapy," which radiate an aura of modernism and therapeutic optimism. With respect to the act of combining antidepressants, the term polypharmacy could be used to describe either the use one of two or more medications within the same broad therapeutic class (i.e., antidepressants) to treat one condition (MDD) or it could even more narrowly be used to describe the use of two medications within the same subclass or with a similar mechanism of action, such as two selective serotonin reuptake inhibitors. In some therapeutic areas of internal medicine, such as the management of hypertension, broad definitions of polypharmacy are obsolete, as it has become the standard of care for physicians to work through hierarchies that might begin with a first-line monotherapy, but quickly move on to different combinations of antihypertensives. The same situation appears to be happening within the pharmacotherapy of depression, where at present there is likely to be consensus only for using the term polypharmacy to describe the simultaneous prescription of two medications with the same mechanism of action.

Tricyclic Plus Monoamine Oxidase Inhibitor Combinations

The treatment landscape for MDD changed dramatically across the last 25 years as a large number of new antidepressants with somewhat differing mechanisms of action or pharmacodynamics profiles were introduced. Prior to the late 1980s, when the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the only major classes of antidepressants available, the decision to prescribe a combination of these medications almost automatically raised red warning flags and, if the practitioner frequently used such combinations, it was only a matter of time before this practice would come to the attention of the peer review authority responsible for ensuring the quality of the prescriber's care. At my institution (now called the University of Pittsburgh Medical Center) at that time, use of antidepressant combinations was one of the standard markers of deviation from the standard of practice. This policy was not a strictly arbitrary practice and generally was not performed to suppress therapeutic creativity: it was commonly accepted that there was no clinical reason to combine two TCAs or two MAOIs and it had been established that it could be dangerous to concurrently prescribe a MAOI and TCA because of the risk of provoking a serotonin syndrome or some related drug-drug interaction. In that era, only the most expert and/or adventurous psychopharmacologists would knowingly use TCA + MAOI combinations and, even then, it was a carefully orchestrated process that followed a particular protocol (e.g., initiate a TCA such as amitriptyline first, titrating to a moderate dose before initiating the MAOI, preferably phenelzine, and slowly titrating to moderate dose). This time-honored approach to co-prescription is still used today, although the proportion of psychiatrists who are able/willing to use TCA + MAOI combinations is no doubt much smaller than it was in, say, 1980!

The reason that some psychopharmacologists even considered combining MAOIs and TCAs—despite the well-known potential hazard of their combination—was the theoretical rationale that these drugs initiated their therapeutic effects on monoaminergic neurotransmission through different, and potentially complementary, mechanisms. Thus, for clinicians following treatment paradigms shaped by the monoamine hypotheses of depression, there was good reason to believe that a depressed patient who was not responsive to a drug that is primarily a norepinephrine reuptake inhibitor, such as desipramine or nortriptyline, might obtain a categorically better response if the neurochemical milieu was "enriched" by a second drug that inhibited enzymatic degradation on monoamines. The fact that the most serotoninergic of all the TCAs, clomipramine, appeared to have the greatest risk of drug-drug interaction when combined with the most potent MAOI, tranylcypromine, simply supported the notion that some combinations could indeed provoke too much of the desired effect.

With 25+ years of hindsight, it is reasonably certain the expert prescribers can safely use TCAs and MAOIs together and that clinical experience suggests that these combinations are sometimes helpful for patients with more advanced forms of treatment resistant depression (see, for example, Berlanga and Ortega-Soto [6]). Nevertheless, this strategy was never extensively studied: to this day there are only a handful of randomized controlled trials (RCTs) in the published literature and none of these studies would actually pass muster as 'adequate' by contemporary standards with respect to research design and statistical power (see, for example, Thase, Trivedi, and Rush [7]). Perhaps most importantly, there is not a single study in which nonresponse to an adequate trial of a TCA or

MAOI monotherapy was established prospectively, nor is there a single study in which the sample size was large enough to have the statistical power to have a reasonable chance to demonstrate that the combination was reliably more effective than one or the other monotherapy. Thus, one is hard pressed to think of a good reason to recommend a combination of a TCA and MAOI prior to first evaluating the potential benefits of these medications alone.

Combining Selective Serotonin Reuptake Inhibitors and TCAs

The modern era of combining antidepressants was heralded by the introduction of the SSRIs, which in the United States began with the approval of fluoxetine in late 1987. The SSRIs of course rapidly replaced the TCAs as the first line antidepressants of choice and, by the mid-1990s, most psychiatrists and many PCPs preferred to initiate antidepressant therapy with either fluoxetine or one of the other widely prescribed members of this class, such as sertraline or paroxetine. Indeed, for more than a decade these three antidepressants were among the most widely prescribed medications in the United States. Such hegemony over the therapeutic landscape was the result of a very strong and clear value proposition: the SSRIs were easier to prescribe, safer, and generally better tolerated than the TCAs, without offering much less in terms of efficacy.

The widespread use of the SSRIs necessarily resulted in a new unmet need in therapeutics, namely, identifying effective strategies for patients with "SSRI-resistant depression". Of course, one possibility was to switch from an SSRI back to an older standard, although it was soon recognized that some patients ran into trouble when trying to quickly taper and discontinue some SSRIs, especially paroxetine, because of discontinuation-emergent somatic symptoms, whereas extreme caution was needed when switching from an SSRI to an MAOI because of a high risk of drug-drug interactions. In the case of fluoxetine, the extremely long elimination half-life of the principal metabolite, norfluoxetine, necessitated up to a 6 week wash-out, which functionally eliminated switching from fluoxetine to an MAOI from practice algorithms. These clinical observations underscored the notion that, whereas switching antidepressants may well be the more heuristically 'pure' strategy, in practice it was often easier to implement adjunctive or combination strategies that might build upon the effects of ongoing SSRI therapy.

One such strategy was suggested by the findings of the comparative treatment literature of the 1980s and early 1990s. Specifically, although the TCAs and SSRIs were generally found to be comparably effective in randomized controlled trials (RCTs), there was evidence from inpatient studies that a subset of TCAs known as tertiary amines, including clomipramine and amitriptyline, may actually be more effective treatments for severe depression [8]. As the most likely explanation for the efficacy advantage for tertiary amine TCAs relative to the SSRIs, but not the more noradrenergically selective secondary amine drugs such as nortriptyline or desipramine, was the former drugs' effects on both noradrenergic and serotoninergic neurotransmission; it was therefore reasonable to consider adding a secondary amine TCA to an ongoing course of SSRI therapy as a means to enhance efficacy.

Early clinical experiences with SSRI + TCA combinations were reassuring in that it was far safer and easier to combine these medications than it was to add an MAOI to a TCA [9]. Although some issues with pharmacokinetic drug–drug interactions arose with some combinations of these drugs, the mechanisms mediating these adverse effects, namely inhibition of CYP450 isoenzymes, were readily addressed by therapeutic drug monitoring and, when necessary, using lower doses of the TCAs. Moreover, some SSRIs, including sertraline and citalopram, had little effect on the metabolic activity of CYP450 isoenzymes such as CYP 2D6 and could be used in combination with TCAs with little risk of pharmacokinetic drug-drug interactions.

Seminal Studies of TCA + SSRI Combinations The most influential of the early reports on TCA + SSRI combinations was that of Nelson and colleagues [10], which was published less than 4 years after fluoxetine was launched in the United States. In this preliminary study, a standardized, albeit open-label, inpatient treatment protocol was used to evaluate the safety and utility of the combination of fluoxetine and desipramine. Although the protocol specified use of therapeutic doses of both medications, serial plasma drug levels were obtained to ensure that the desipramine dose was in a targeted therapeutic range. A total of 14 MDD patients were treated according to this protocol and their outcomes were compared to a historical control group consisting of 42 MDD inpatients who were treated previously on the same unit with desipramine monotherapy (average dose: 175 mg/day). Patients in the combined therapy case series received fluoxetine 20 mg/day in addition to desipramine (median dose: 125 mg/day) and were significantly more likely to benefit from treatment, with a week 4 remission rate of 71 % compared to 14 % in the control group. Beyond the methodological issues linked to the open and nonrandomized nature of the case series, which would be expected to inflate perceptions of benefit, the combined therapy group also had significantly higher desipramine plasma levels, despite serial dose adjustment, which might have influenced response rates. Nevertheless, the magnitude of the difference between these groups was so large that this combination appeared to be a very promising strategy.

The results of subsequent studies have not been so clear-cut. In fact, only one of three RCTs evaluating the desipramine

+ fluoxetine combination has yielded supportive efficacy findings. In the first study, a small multi-center trial [11], 41 outpatients with MDD who had not responded to a prospective, 8-week course of fluoxetine monotherapy (20 mg/day) were randomized to receive 4 weeks of additional double blind therapy with one of the three following options: 1) fluoxetine, with the dose increased to 40 to 60 mg/day; 2) fluoxetine 20 mg/day plus desipramine 25 to 50 mg/day; or 3) fluoxetine 20 mg/day plus lithium 300 to 600 mg per day. As all three of these strategies were potentially effective options, this study had no true control group and, as such, statistical significance would require that one active option was clearly superior to the others. Moreover, with only about 17 patients per treatment arm, adequate statistical power was only available to find extremely large (e.g., >50 %)—and very unlikely—differences between the treatments. Thus, the main finding, namely that no significant differences were found, was not surprising. It was potentially noteworthy that, when numeric trends were noted, they consistently favored the group that was treated with higher doses of fluoxetine over the groups receiving combined antidepressants or lithium augmentation. For example, the group that received higher dose fluoxetine therapy had a 53 % remission rate, as compared to a 25 % remission rate for the group that received the fluoxetine + desipramine combination and a 29 % remission rate for the group that received lithium augmentation of fluoxetine. A second, larger study (n=101) using the same protocol was subsequently completed and, again, no clear advantage was found for combining these doses of fluoxetine and desipramine as compared to simply increasing the dose of fluoxetine [12]. When considered together, these studies clearly demonstrated that, for patients who did not benefit from lower dose SSRI therapy, it was not particularly helpful to add low doses of desipramine.

One way to reconcile the exciting preliminary findings of Nelson et al. [10] and the subsequent, dispiriting results of Fava et al. [11, 12] is to focus on the dose of desipramine and the potential importance of therapeutic drug monitoring. Given that TCAs do have dose-response relationships, it is not trivial that Nelson and colleagues [10] used more than twice the dose of desipramine and employed therapeutic drug monitoring to ensure that plasma levels were within the therapeutic range. The results of the third controlled study of the fluoxetine + desipramine combination, conducted by Nelson and colleagues [13], specifically address these issues. In this trial, 39 inpatients with MDD were randomly assigned to 6 weeks of double blind treatment with: 1) fluoxetine monotherapy, 20 mg/day; 2) desipramine monotherapy, average dose 294 mg/day; or 3) combined therapy (fluoxetine 20 mg/day + desipramine 98 mg/day). The large disparity in desipramine doses reflects the fact that the protocol used an unblinded monitor to ensure that the plasma levels of the two groups were matched within a specified therapeutic range to the extent that was possible. Nelson and colleagues found strong evidence in favor of the fluoxetine + desipramine combination. For example, whereas the groups receiving fluoxetine and desipramine monotherapies had remission rates of 7 % and 0 %, respectively, the group treated with the combination achieved a 54 % remission. These findings strongly suggest that one must ensure that the plasma levels of the TCA are fully within the therapeutic range in order to capitalize on the potential merits of this combination therapy.

Combining SSRIs and Bupropion

As clinicians were gaining experience using combinations of fluoxetine and TCAs, the novel, non-serotoninergic antidepressant bupropion was reintroduced in the United States in 1989. Bupropion is classified as a norepinephrine dopamine reuptake inhibitor, although the results of PET studies utilizing transporter imaging methods have raised questions about the potential clinical significance of the relatively small magnitude of effects on dopamine neurotransmission [14, 15]. By the end of the 1990s, bupropion had largely replaced the TCAs as the drug of choice for combining with SSRIs. Bupropion supplanted the TCAs for several reasons, including a better overall safety profile and a virtual absence of sexual side effects. The groundswell of clinical enthusiasm for combining bupropion and SSRIs was not supported by data from well-controlled trials and, across the past decade, the state of the evidence has only marginally improved.

There have been three randomized studies of SSRI + bupropion strategies utilizing active comparators [16, 17, 18••]. In the first, a multicenter trial conducted in Canada, Lam and colleagues [16] studied MDD patients who had a past history of nonresponse to at least one adequate trial of antidepressant therapy and prospective nonresponse to a trial of either the SSRI citalopram or bupropion sustained release (SR). The choice of drugs for the prospective trial was left up to the treating clinician. Next, the 61 patients who did not respond to monotherapy were allocated to either the combination of citalopram and bupropion SR (n=32) or a switch to another course of monotherapy with the alternate medication (n=29). For logistical reasons the investigators did not use conventional random assignment to treatment, but instead used a quasi-randomization method based on alternating study months. With respect to the primary outcome, response rates, they found that the group receiving combination therapy was somewhat more likely to respond (56 %) than the group receiving the alternate monotherapy (38 %), although this potentially meaningful 18 % between-group difference was not statistically significant. A slightly larger trend likewise favored the combination strategy for remission rates: 28 % versus 7 %. A statistically significant difference was found on

a key secondary endpoint, reduction of depressive symptoms. The combination was also reasonably well tolerated and attrition from the combination strategy was no greater than observed with the monotherapy.

The second comparison was conducted as part of the large multicenter US study known as STAR*D [17]. In STAR*D, the combination of citalopram and bupropion SR was evaluated in patients who had not remitted despite a vigorous trial of citalopram monotherapy (i.e., up to 60 mg/day across up to 14 weeks) [13]. One of the aims of STAR*D was to approximate "real world" conditions and, as such, treatments were studied in both primary care and psychiatry settings using open label (unblinded) delivery of treatment and independent (blinded) clinical evaluators. The citalopram + bupropion combination was studied in the second level of the study, using an equipoise-stratified randomization scheme was used to allocate approximately 1200 patients across seven strategies; four of the strategies involved switching treatments and three of the strategies were adjunctive/combining approaches. Although the STAR*D investigators had intended to directly compare the switching and adjunctive/combining strategies, the randomization procedure did not work as planned and too few patients accepted randomization across all of the strata to permit the planned comparisons. Thus, the combination of citalopram and bupropion could only be compared to the combination of citalopram and the anxiolytic buspirone, not to bupropion monotherapy or any of the other switching strategies. A total of 565 patients who had not remitted with citalopram monotherapy allocated to these arms, making this the largest study of combined antidepressant treatment ever undertaken at the time. Moreover, the STAR*D investigators had not expected the adjunctive buspirone therapy option to be particularly effective and, as such, it could be thought of as a proxy for an active placebo. With these caveats in mind, the lack of significant differences between the two groups does not engender great confidence in the utility of the SSRI + bupropion combination. That said, the combination of citalopram and bupropion was well tolerated and there was a small, but statistically significant advantage for the combined antidepressant therapy group on the self-report version of the Quick Inventory of Depressive Symptomatology and secondary *post hoc* analyses using a novel psychometric approach similarly confirmed a small advantage of for the antidepressant combination relative to citalopram + buspirone [19].

The third comparison of the combination of an SSRI and bupropion SR was conducted as part of the COMED study [18••]. This study, which was conducted by a subgroup of the STAR*D investigators, tested the hypothesis that combined therapy might actually accelerate response or lead to better outcomes from the initiation of therapy. A total of 665 patients were randomized to 12 weeks of treatment in one of three arms: 1) the SSRI escitalopram (10–20 mg/day) plus single blind placebo; 2) escitalopram (10–20 mg/day) plus bupropion SR (150–400 mg/day); or 3) the combination of the SNRI venlafaxine extended release (ER) and mirtazapine. Treatment was openly adjusted and outcomes were assessed single blind by an independent evaluator. The planned comparisons involving the third arm will be discussed in the next section.

With respect to the contrasts between SSRI + placebo and the SSRI + bupropion SR combination, remission rates were almost identical (about 39 % for both groups) and there were no differences between the groups with respect to speed of response or reductions in depressive symptom scores. Interestingly, despite using an identical protocol, patients in the escitalopram + placebo arm received a more vigorously titration of the SSRI (mean dose: 17.6 mg/day) than did those in the combination therapy group (mean escitalopram dose: 12.8 mg/day). Thinking back to one of the key findings gleaned from the studies of desipramine and fluoxetine, it may be that one must be willing to use full or maximal doses of both the bupropion and the SSRI if one hopes to capitalize on their combined therapeutic potential.

Combining SSRIs/SNRIs and Mirtazapine

The tetracyclic compound mirtazapine is relatively unique because it is one of the few modern antidepressants to have no direct effects on monoamine uptake transporters. The antidepressant effects of mirtazapine are thought to result from simultaneous modulation of noradrenergic and serotoninergic neurotransmission by antagonism of alpha-2 autoreceptors and heteroceptors and blockade of post-synaptic serotonin 2 and 3 receptors. Mirtazapine also has the most potent antihistaminergic effects of all the modern antidepressants, although this effect may have more to do with characterizing the side effect profile of this drug than its antidepressant MOA. When compared to the SSRIs, mirtazapine monotherapy was shown to be comparably effective, overall, with a somewhat more rapid onset of action [20]. Mirtazapine also had a more favorable effect on sleep disturbances than the SSRIs, although it was more likely to cause sedation and weight gain [20]. From the time of introduction, it was suspected that the combination of mirtazapine and SSRIs might have some synergistic or additive effects by virtue of both complementary symptomatic effects and, perhaps, lessening of particular side effects associated with serotonin reuptake inhibition; case reports of combinations of mirtazapine and other antidepressants rapidly emerged following its introduction in the mid-1990s and Stahl even suggested that mirtazapine was a critical component of a three drug antidepressant combination that he named California Rocket Fuel (see Thase [5]).

The literature contains a limited amount of support for the utility of mirtazapine combined with SSRIs and SNRIs. The

first study to evaluate mirtazapine combination therapy studied 26 outpatients with a history on nonresponse to at least one adequate course of antidepressant therapy [21]. Patients continued to take the ineffective primary antidepressant (primarily SSRIs) and were randomized to receive either active mirtazapine (15–30 mg/day) or a double blind placebo. After 4 weeks of therapy, the group receiving the adjunctive mirtazapine had a significantly greater reduction in depressive symptoms than the group receiving a placebo adjunct to ongoing antidepressant therapy. The remission rates were 45 % and 13 %.

The second study to evaluate this particular combination tested the hypothesis that SSRI + mirtazapine would produce a faster or more dramatic response than monotherapy from the outset of treatment [22]. In this trial, 61 outpatients with MDD were randomized to 6 weeks of double-blind therapy with: 1) mirtazapine (30–60 mg/day); 2) paroxetine (20–40 mg/day); or 3) mirtazapine plus paroxetine. When compared to the monotherapies, the combination of mirtazapine plus paroxetine was reasonably well-tolerated and did not result in significantly greater attrition. The combined treatment group also experienced a significantly larger reduction in depression symptom scores than the monotherapy groups. At week 6, remission rates were 43 %, 19 %, and 26 % for the combined, mirtazapine alone, and paroxetine alone groups. These potentially meaningful between-group differences were not statistically significant in a study of this size.

A subsequent larger study (N=105) [23••] led by the same principal investigator randomly assigned patients to receive 6 weeks of therapy with: 1) fluoxetine (20 mg/day) plus placebo; 2) fluoxetine (20 mg/day) in combination with mirtazapine (30 mg daily); 3) mirtazapine(30 mg/day) in combination with venlafaxine (225 mg/day); or 4) mirtazapine (30 mg/day) in combination with bupropion (150 mg/day). This study again tested the hypothesis that patients receiving combination antidepressant therapy would show a more rapid or more complete remission from the outset of therapy. For this study, the group receiving fluoxetine plus placebo served as the basis of comparison; this group had a week 6 remission rate of 25 %. By contrast, all three of the combination therapy groups had superior outcomes, with remission rates of 52 %, 58 %, and 46 % for the groups receiving fluoxetine, venlafaxine, and bupropion, respectively. The side effect burdens associated with the 3 combination strategies were not markedly worse than what was observed in the fluoxetine plus placebo group and there were no significant differences in attrition from the treatment protocol.

Two other studies evaluated the combination of mirtazapine and venlafaxine. One evaluated the combination of mirtazapine and venlafaxine as a "fourth step therapy" in the multistage STAR*D trial [24]. As with the other STAR*D comparisons, this trial involved open-label administration of study medications and independent assessments by clinical evaluators who were not aware of the treatment assignment. A total of 109 patients who had not responded to three sequential treatment trials were randomly assigned to treatment with either the AD combination (mirtazapine, mean dosage 36 mg daily; venlafaxine extended release, mean dosage 210 mg daily) or the MAOI tranylcypromine (mean dosage, 37 mg daily). Some portion of the study group had not responded to mirtazapine and (or) venlafaxine monotherapy during earlier stages of the study, although this unreported number was likely to be small and insufficient for secondary analyses. At the end of 12 weeks of treatment, neither treatment strategy was particularly effective, with final remission rates of 7 % and 14 % for the tranylcypromine and combination therapy groups, respectively. Nevertheless, the combination strategy was associated with significantly greater reduction of depressive symptoms and significantly less attrition, owing to side effects. These findings suggest that the combination of venlafaxine and mirtazapine has certain advantages, compared with tranylcypromine, for patients with more advanced grades of treatment resistant depression who have not benefited adequately from several prior treatments. This conclusion is limited by the relatively low average dose of tranylcypromine, which indicates that less than one-half of the patients who received this therapy actually took an adequate dose of medication. An additional conclusion suggested by this latter finding is that clinicians in contemporary practice are better able to implement a trial of combination therapy with newer-generation ADs than they are able to implement an adequate trial with an MAOI.

The second comparison was conducted as part of the COMED trial [18••], which—as described earlier—evaluated whether combination therapy could speed or enhance recovery rates from the outset of therapy, using escitalopram + placebo as the standard of comparison. A total of 220 COMED patients were randomized to receive the combination of venlafaxine (final mean dose: 178 mg/day) and mirtazapine (final mean dose: 18 mg/day). The outcome of the group was essentially identical to that of the escitalopram + placebo group across 12 weeks of therapy. For example, the combined group had a remission rate of 38 % compared to the 39 % remission rate of the escitalopram plus placebo group and both groups had 52 % response rates. Although dropout rates also were similar, the combined group did report a significantly greater side effect burden. Thus, it seems likely that if one tried to enhance the efficacy of this combination by increase further the doses of one or the other of the components, an even greater disadvantage in tolerability would have been evident. In short, the COMED study provided no evidence to support the decision to begin antidepressant medications from the outset of therapy.

Conclusions

The paucity of well-controlled studies of combined antidepressant strategies, coupled with inconsistencies in the

findings of the studies that have been completed, justify the conclusion that this commonly used approach has not been adequately researched. That most of the studies suggest that combining antidepressants of dissimilar structure and mechanism of action may convey some greater benefit (compared with monotherapies), coupled with the need for more effective treatments for our depressed outpatients, certainly provides a strong justification for further research on this topic.

Despite the need for more research, there are two good reasons to continue to use antidepressant combinations in clinical practice: 1) there is a clear need for alternate treatments for patients who do not respond to our standard first and second line medications and 2) the flow from the "pipeline" that delivers unique antidepressants that could truly help those who are not helped by our current standards has, at least temporarily, slowed to a trickle.

As a clinical researcher, I accept that there will never be sufficient resources to support enough well controlled studies to be conducted to adequately answer all of the important questions in our area of therapeutics. As a practitioner, I likewise accept that it is not possible to fully apply the principles of evidence based medicine when I must make decisions about whether or not to combine two antidepressant medications. Thus, despite the "less than desired" amount of data from large, well-controlled studies and a complete lack of FDA approval for any particular antidepressant combination, I do use antidepressant combinations under some circumstances in my practice. The most rational combinations of antidepressants involve medications that have dissimilar mechanisms of action, such as bupropion and an SSRI or venlafaxine and mirtazapine. One might interpret from the existing evidence that it is necessary to use fully therapeutic doses of both medications in order to maximize the efficacy of the combination. The safety of such a combination is increased by picking medications that either do not have pharmacokinetic interactions or whose interactions can be monitored or even capitalized by therapeutic drug monitoring. The use of such rational drug combinations should not be used to the exclusion of both older (e.g., lithium) and newer (e.g., second generation antipsychotics such as aripiprazole and quetiapine) adjunctive therapies with proven efficacy or time-tested older therapies such as the TCAs or MAOIs.

Compliance with Ethics Guidelines

Conflict of Interest Michael E. Thase has provided scientific consultation to Alkermes, AstraZeneca, Bristol-Myers Squibb, Dey Pharma, Eli Lilly & Company, Forest Pharmaceuticals, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Merck and Co., Neuronetics, Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, Pfizer (formerly Wyeth-Ayerst Laboratories), Schering-Plough (formerly Organon), Shire US, Sunovion Pharmaceuticals, Takeda (Lundbeck), and Transcept Pharmaceuticals. Dr. Thase receives grant funding from the Agency for Healthcare Research and Quality, Eli Lilly & Company, GlaxoSmithKline (ended 7/10/2013), National Institute of Mental Health, Otsuka, and Sepracor. He has equity holdings in MedAvante and receives royalties from American Psychiatric Foundation, Guilford Publications, Herald House, Oxford University Press, and W.W. Norton & Company. His wife is employed as the Group Scientific Director for Embryon (formerly Advogent; Embyron does business with Bristol-Myers Squibb and Pfizer/Wyeth).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. • Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67(1):26–36. This article provides evidence about temporal changes in treatment selection and documents the prevalence of combining antidepressants.
2. • Richelson E. Multi-modality: a new approach for the treatment of major depressive disorder. Int J Neuropsychopharmacol. 2013;30:1–10. A good summary of the rationale for combining antidepressants and the pros and cons of monotherapy versus combination therapy.
3. Rush AJ. Combining antidepressant medications: a good idea? Am J Psychiatry. 2010;167(3):241–3.
4. Preskorn SH, Lacey RL. Polypharmacy: when is it rational? J Psychiatr Pract. 2007;13(2):97–105.
5. Thase ME. Antidepressant combinations: widely used, but far from empirically validated. Can J Psychiatry. 2011;56(6):317–23.
6. Berlanga C, Ortega-Soto HA. A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination. J Affect Disord. 1995;34(3):187–92.
7. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology. 1995;12(3):185–219.
8. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety. 1998;7 Suppl 1:11–7.
9. Lam RW, Wan DD, Cohen NL, Kennedy SH. Combining antidepressants for treatment-resistant depression: a review. J Clin Psychiatry. 2002;63(8):685–93.
10. Nelson JC, Mazure CM, Bowers Jr MB, Jatlow PI. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry. 1991;48(4):303–7.
11. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry. 1994;151(9):1372–4.
12. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol. 2002;22(4):379–87.
13. Nelson JC, Mazure CM, Jatlow PI, Bowers Jr MB, Price LH. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry. 2004;55(3):296–300.

14. Meyer JH, Goulding VS, Wilson AA, Hussey D, Christensen BK, Houle S. Bupropion occupancy of the dopamine transporter is low during clinical treatment. Psychopharmacology (Berl). 2002;163(1): 102–5.
15. Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B. In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. Biol Psychiatry. 2003;54(8):800–5.
16. Lam RW, Hossie H, Solomons K, Yatham LN. Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry. 2004;65(3):337–40.
17. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006;354(12):1243–52.
18. •• Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry. 2011;168(7):689–701. A very important randomized trial evaluating whether antidepressant combinations might accelerate remission or improve outcomes if used from the outset of therapy. This large multicenter study found no evidence to support the use of combined therapy from the outset of treatment.
19. Bech P, Fava M, Trivedi MH, Wisniewski SR, Rush AJ. Outcomes on the pharmacopsychometric triangle in bupropion-SR vs. buspirone augmentation of citalopram in the STAR*D trial. Acta Psychiatr Scand. 2012;125(4):342–8.
20. Thase ME, Nierenberg AA, Vrijland P, van Oers HJ, Schutte AJ, Simmons JH. Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. Int Clin Psychopharmacol. 2010;25(4):189–98.
21. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry. 2002;51(2):183–8.
22. Blier P, Gobbi G, Turcotte JE, de Montigny C, Boucher N, Hébert C, et al. Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. Eur Neuropsychopharmacol. 2009;19:457–65.
23. •• Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. Am J Psychiatry. 2010;167(3):281–8. In contrast to the findings of COMED, this single center study found that vigorously dosed combinations were more effective than monotherapy with fluoxetine.
24. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry. 2006;163(9): 1531–41.