

# Augmentation and Combination Pharmacotherapy Trends in Major Depressive Disorder Results of a Brief Survey of Psychiatrists

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## ABSTRACT

Major Depressive Disorder is often a difficult-to-treat mental illness. Despite success for some patients with monotherapy, many patients do not achieve full remission from their symptoms, and they are classified as treatment-resistant. Combination/augmentation strategies, as a result, appear to have become a common practice among psychiatrists, despite a relative lack of randomized, controlled data in this area.

In this article, we summarize the results of a brief survey in a sample of convenience of 601 psychiatrists about their prescribing practices throughout the course of treating depressed patients. Our survey revealed that selective serotonin reuptake inhibitors (SSRIs) are the usual first-line drugs for depression management and that selective serotonin–norepinephrine reuptake inhibitors (SNRIs) are usually the first drugs patients are switched to when initial monotherapy fails. The most commonly used augmentation strategy is the addition of lithium, and the most common combination strategy is the addition of bupropion. Second-line and third-line treatment choices are also outlined.

Our findings should help to define current practices of combination/augmentation pharmacotherapy for depressed patients. This naturalistic information is important because it may be used to generate more stringent, outcomes-based trials in the future.

**Key words:** antidepressants, augmentation, combination, depression

## INTRODUCTION

Depression is a socially debilitating illness, sometimes lifelong, that afflicts the U.S. population with an estimated lifetime risk of 16%.<sup>1</sup> Unfortunately, only a third of depressed patients are receiving any form of treatment, and among the ones who are, only one half to two thirds ever achieve a full response to therapy.<sup>2</sup>

Treatment-resistant depression, unfortunately, is quite common in clinical practice, and the failure to achieve an adequate response in 50% to 60% of patients after at least one trial of an antidepressant of sufficient dose and duration also seems to be commonplace.<sup>3</sup> In order to improve therapeutic effectiveness of monotherapy with the ultimate aim of achieving and maintaining remission, additional methods are often employed in clinical psychopharmacology, including augmentation and combination therapies.

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## Monotherapy Approach

Before we discuss these practices, we will summarize the usual monotherapy practices. To date, there are no discrete national guidelines to delineate the stepwise treatment of resistant depression, although many local and regional practices are followed. Available treatment guidelines for depression from various geographical regions and organizations usually assume that a patient is antidepressant-naive and is starting out without prior intervention. We will discuss the usual stepwise approach for depression treatment with this in mind. Actually, many patients do have pre-existing depression and may already be receiving treatment when they are first seen in the office. This scenario may be considered to be an initially treatment-resistant state.

## First-Line Therapy

The term “first-line” may have multiple meanings. One definition suggests that an antidepressant agent should be used first because of its clinical efficacy, its safety, or both. Most often, effectiveness is comparable between first-line and second-line drugs, but safety is improved with the first-line agents. In rare instances, a second-line drug may have better efficacy but may be associated with too many adverse effects to warrant a first-line use.

The second definition of a first-line drug, which we do not use in this article, is usually dictated by managed care insurance agencies when they declare an agent to be “first-line.” This definition is often based on a third variable, cost.

Since the 1980s, the selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (Prozac, Eli Lilly) sertraline (Zoloft, Pfizer), paroxetine (Paxil, GlaxoSmithKline), citalopram hydrobromide (Celexa, Forest), and escitalopram oxalate (Lexapro, Forest), have become first-line medications because they are safer than the older tricyclic antidepressants (TCAs). The Food and Drug Administration (FDA) suggests that the TCAs and SSRIs are comparable in efficacy, based on usual approval standards, which evaluate each drug’s ability to lower the severity of depression by 50% or better (a “response”). However, more clinical evidence-based data have suggested that TCAs are more effective in promoting a “remission” of symptoms (more than 70% improvement).<sup>4,5</sup>

## Second-Line Therapy

It has been postulated that either the tricyclic molecule is superior to SSRIs or, more likely, that the TCAs often elevate levels of norepinephrine plus serotonin—which itself may be a

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polypharmacy approach. If the SSRIs fail to relieve depression, the patient is usually switched to a “second-line” agent. These medications are often the selective serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine (Effexor, Wyeth) and duloxetine (Cymbalta, Eli Lilly) or a norepinephrine–dopamine reuptake inhibitor (NDRI), such as bupropion (Wellbutrin, GlaxoSmithKline).<sup>2</sup>

The idea is to switch from a serotonin-only agent to a new class of drugs that manipulates a different set of neurotransmitters. On the other hand, it may still be common practice to switch from one SSRI to another, because of individual variability in responses to the different SSRIs. It is possible that it is just the added duration of serotonin manipulation that produces efficacy instead of the perceived variability among the SSRIs, all of which have the same mechanism of action.

### Third-Line Therapy

“Third-line” antidepressants may include the TCAs, monoamine oxidase inhibitors (MAOIs), or combinations of the aforementioned drugs. Third-line drugs are considered to be associated with an increased risk because of their adverse event profile. In clinical practice, it appears that primary care physicians often use this stepwise approach, and psychiatrists more often start with second-line agents or combine agents more quickly than in the third step noted here.<sup>6,7</sup> Again, the idea is to manipulate multiple neurotransmitters for better efficacy.

### Combination/Augmentation Therapy

Combination/augmentation approaches in major depression often appear to have clinical benefits; however, there are some factors to consider before one takes this step.

First of all, every drug has adverse effects, and the addition of multiple agents may result in even more of a side-effect burden. As the number of drugs taken increases, patient adherence and compliance often decrease. There is evidence that depressed patients who stop their medications too quickly relapse into depression more often.<sup>8</sup> Sometimes augmentation/combination strategies allow a “win–win” situation when the two agents improve efficacy and decrease each other’s side effects. An example might include the addition of bupropion to an SSRI. Bupropion may add effectiveness and symptom relief and, at the same time, may reduce weight gain and sexual dysfunction induced by the original SSRI that was used.

Cost may become important as the number of medications used increases. Polypharmacy generally costs patients and society more money. Drug prices per patient increase, as does the use of health care resources to manage these complex regimens and their potential side effects. Many health care insurance agencies take issue with polypharmacy practices, because there are often almost no randomized trials of significant power to prove that complex regimens work. Even though many clinicians use combination/augmentation approaches in psychiatry and other medical areas, subjective reports and small and lower-powered studies do not usually carry weight in most health plans.

Augmentation of initial monotherapy refers to the addition of a non-FDA-approved (“off-label”) agent with counterdepressive qualities, whereas combination therapy consists of the addi-

tion of a second FDA-approved antidepressant.<sup>3</sup> The use of multiple agents with different variations inherent in individual psychiatric practice has led to combinations and augmentations being the perceived and probable standard of care.<sup>9,10</sup> The variability among individual psychiatrists in terms of their prescribing habits in managing major depression is still unmeasured; hence, conclusive data regarding the impact on achieving and maintaining remission cannot be adequately determined.

One current trend in the marketplace is a demand for the development of new drugs that can embody “polypharmacy in a single pill.” Preliminary reports and abstracts suggest that the newest wave of antidepressants may be the “triple reuptake inhibitors”—single drugs with the ability to elevate serotonin, norepinephrine, and dopamine levels simultaneously (*PR Newswire*, June 27, 2005). Currently, a physician would have to combine two or three drugs to achieve this effect in a patient.

Bristol-Myers Squibb gained FDA approval for the selegiline (Emsam) MAOI patch, and at higher doses, all three monoamines would be simultaneously elevated via MAO inhibition for the treatment of depression.<sup>11,12</sup>

In order to determine the prevailing strategies in combination/augmentation therapy for Major Depressive Disorder (MDD), given the ambiguity and variability of evidence-based medicine in this area, we surveyed a group of international psychiatrists. We did not study the outcomes of their practices because of the sample of convenience method applied.

## MATERIALS AND METHODS

At the 2005 American Psychiatric Association Annual Meeting in Atlanta, Georgia, an interactive symposium, entitled “Treating Depressive Illnesses: Evidence-Based Updates,” was presented on the topic of the treatment of MDD. One lecturer and co-author (Dr. Schwartz) used an audience-response keypad system to ask the 601-member audience of international psychiatric practitioners about their individual pharmacological practices for their MDD patients.

For any single question, it would be expected that 10% of the 601 participants would be non-responders. Ninety percent of the participants in this sample of convenience were prescribing psychiatrists from the U.S. and abroad. Prior to receiving the participants’ responses, the investigator verbally polled the audience members about the frequency with which they used polypharmacy in treating their patients with unipolar depression.

Because of this naturalistic sample, we could not categorize the psychiatrists according to their age, sex, number of years in practice, or other demographic data. There were no *a priori* research questions, because the data gathered were to be used as a teaching tool. Questions about usual prescribing strategies in treatment-resistant patients were projected on the screen initially (see Results). Subsequently, audience real-time answers were presented on the screen and were used at this symposium as a learning tool during the lecture.

This interactive system was used to increase learning and among symposium participants. It was also designed to share with the audience the tendency toward combination/augmentation strategies in MDD. Participants read the questions and were given about 10 seconds to formulate an answer. The statistical analysis used simple descriptive measures. The percentages of responses are presented in Figures 1 to 4.

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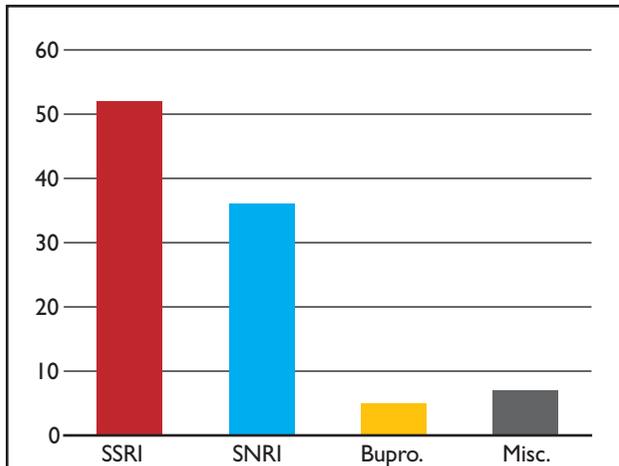


Figure 1 Results of the following question posed to an audience of psychiatrists at the 2005 APA meeting: "For an initial depressive episode, which antidepressant are you most likely to choose?" Bupro. = bupropion; Misc. = miscellaneous; SNRI = selective serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

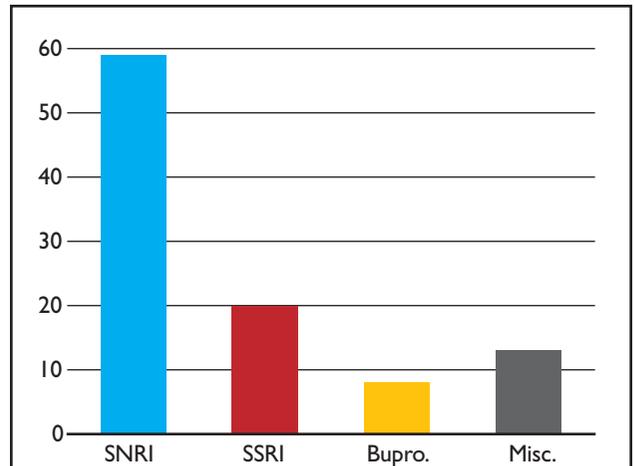


Figure 2 Results of the following question posed to an audience of psychiatrists at the 2005 APA meeting: "For a patient failing [to respond to] initial SSRI treatment in an initial depressive episode, which antidepressant are you most likely to switch to?" Bupro. = bupropion; Misc. = miscellaneous; SNRI = selective serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

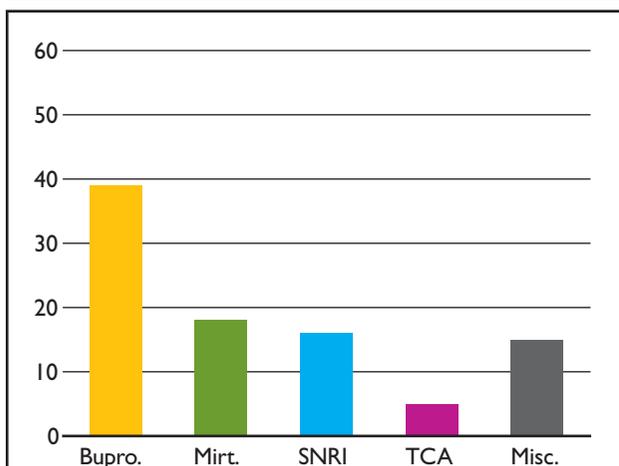


Figure 3 Results of the following question posed to an audience of psychiatrists at the 2005 APA meeting: "If you were to see a patient in his/her third depressive episode who was [using] an SSRI, which FDA-approved antidepressant would you choose to combine for better efficacy?" Bupro. = bupropion; Mirt. = mirtazapine (Remeron); TCA = tricyclic antidepressant; Misc. = miscellaneous; SNRI = selective serotonin–norepinephrine reuptake inhibitor.

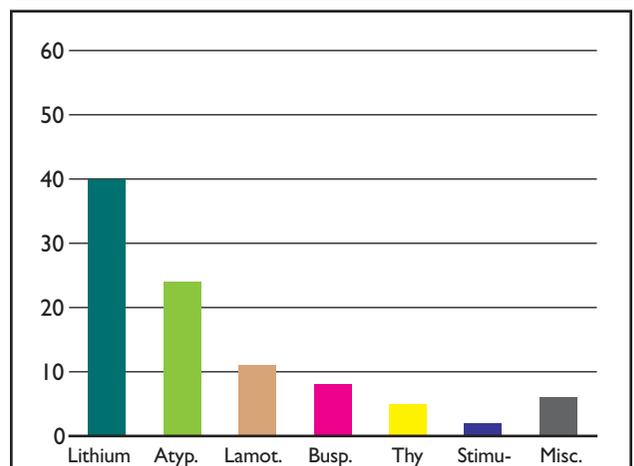


Figure 4 Results of the following question posed to an audience of psychiatrists at the 2005 APA meeting: "If you were to see a patient in his/her third depressive episode who was [using] an SSRI, which drug (not FDA-approved for depression) would you choose to augment [therapy] with for better efficacy?" Atyp. = atypical antidepressant; Busp. = buspirone (Buspar); Lamot. = lamotrigine (Lamictal); Misc. = miscellaneous; Thy hor. = thyroid hormone.

### RESULTS

Our initial verbal polling of the audience suggested that the "usual" depressed patient in clinical practice would receive two or three psychotropic drugs at any given time after sequential administration. It was clear, among the psychiatrists in the room, that we could not adequately define an "average" depressed patient; however, the question posed suggested that participants focus on depressed patients without major comorbidities.

With this baseline information as a starting point for the lecture, scenarios of clinical depression were presented to the audience, and their usual practices were elicited by the audience response pad system (see Figures 1 to 4). The immediate rate of audience responses to the questions was, on average, above 80%, suggesting that an adequate number of audience members participated. The questions and answers are presented in the figures.

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## DISCUSSION

Because the survey results were obtained from a select population of psychiatrists, it is evident that combination and augmentation techniques are commonly used in treating MDD patients. The use of this complex pharmacotherapy has probably developed as a result of attempts by clinicians to treat depressive patients until they achieve remission. It is interesting that there is a limited base of evidence available to fully support this practice. Only a few randomized, controlled trials have been conducted, and many of the studies are small and open-label. In fact, the most stringent positive augmentation studies involve lithium, which may also have the least favorable side-effect profile.

It seems reasonable to base one's clinical practice on the evidence at hand, but when these data are not available, understanding the practices of one's colleagues may be very useful. In theory, if a majority of psychopharmacologists are using a certain set of medications for most of their MDD patients, this might be tentatively interpreted as an effective and safe strategy. These naturalistic data could be used to empirically support continued combination/augmentation practices, especially if future prospective studies are focused on validating outcome-based findings.

## LIMITATIONS OF THE STUDY

Our survey had several limitations. Participants in a lecture setting might respond in a group setting differently than if they were given a written survey in a private setting. Responders may answer in such a way as to try to please the presenter, for example. Also, because each clinician's definition of a "usual" depressed patient might vary, our findings might not be applicable in all patient subpopulations.

Finally, in a convenience sample, the patients are selected at the convenience of the researcher, with little attempt made to ensure an accurate representation of a larger group.

## CONCLUSION

As was noted in the sample of convenience described in this article, combination and augmentation techniques are commonly used in treating depressed patients. With these strategies, it seems possible that the pharmaceutical industry is moving away from drugs with a single mechanism of action (i.e., the SSRIs) and may be leaning toward triple reuptake inhibitors; the FDA has approved new MAOIs, in which norepinephrine, serotonin, and dopamine can be combined in one tablet instead of two or three separate tablets.

Researchers should also start to develop studies in which simultaneous applications of multiple medications are used instead of the usual stepwise monotherapy approach. Although

it would be critical to conduct large prospective studies of novel augmentation/combination strategies, the number of subjects needed to power such a study could be prohibitive. It is possible that naturalistic practices, such as those outlined in this article, are driving drug development and may lead to future FDA-approved polypharmacy in a single pill.

A more scientifically stringent base of evidence would be welcome, and it is hoped that such evidence will be supportive of this practice.

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