

Introduction

Augmentation of Antidepressant Medication

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Eight new antidepressants have been introduced in the past decade (Table 1). The improved safety, tolerability, and perceived effectiveness of these medications have dramatically increased public awareness of depression as a serious illness and have contributed to the increase in acceptance of medication as a treatment modality. Despite advances in the diagnosis and treatment of depressive illness, the outcome of pharmacotherapy remains unsatisfactory for many patients.

Apart from side effects, there are two major limitations of antidepressant therapy. One is the delayed onset of improvement. The lag between the start of treatment and the onset of therapeutic activity appears to characterize all antidepressant drugs. In fact, a minority of patients do report feeling better within a few days. More typically, it takes several weeks for a significant response to be noted. During this interval, the patient remains distressed, impaired, and at risk for suicide. Noncompliance also becomes more likely.

The second limitation is partial response. Even among those who complete an adequate trial of antidepressant medication, only about half can expect to have a full response. However, the degree of the antidepressant response can vary so that apart from complete resolution of symptoms, partial response may occur. In general, 25% of those who receive an antidepressant continue to manifest residual symptoms. Thus, there continues to be a need for alternative approaches that are more universally effective or that would benefit particular patients refractory to existing antidepressant drugs.

In order to address these clinical dilemmas, psychiatrists have resorted to monotherapy with unconventional agents, such as clozapine and buprenorphine. These measures, like electroconvulsive therapy, are generally reserved for truly refractory patients. However, for those patients who fail to improve after full initial therapeutic trials with one or two

primary antidepressants, psychiatrists more commonly employ add-on therapy to enhance response.

In the past, the practice of using multiple drugs to enhance treatment response was called *polypharmacy*, and was disparaged as poor clinical practice. However, with improved understanding of how drugs affect the central nervous system and increased communication in journals and on computer networks about the relative merits of specific combinations, the scientific basis for combining drugs is being defined. Indeed, the use of multiple medications as a strategy to enhance response has become both acceptable and widespread. It is now referred to more positively as *add-on therapy*, *co-medication*, *combination therapy*, or *drug augmentation*.

REASONS TO USE AUGMENTATION

Augmentation addresses several dimensions of response to treatment. These dimensions are (1) speed of response, (2) degree of response, and (3) duration of response. It does not include the mitigation of drug side effects or symptomatic treatment of depressive symptoms, such as insomnia or anxiety.

Whatever the strategy used, it is generally agreed that the goal of treatment should be to produce complete resolution of the acute episode of depression. The reasons for this include the findings that incomplete remission of a primary depression is associated with chronicity and increased risk of relapse, greater functional impairment, and higher risk of suicide.

PRETREATMENT CONSIDERATIONS

Before undertaking augmentation strategies, several measures should be implemented. Care should be taken to confirm that the patient has had an adequate antidepressant trial. A patient who comes in with a long list of medications tried without effect often has been taking them for just a few days, often at inadequate doses. Patients who are unable to comply with outpatient trials of adequate duration and dose should be medicated as inpatients. Failure of multiple therapies should prompt a reassessment of the working diagnosis as well as consideration of whether concurrent mental disorders exist. The possibility that a patient is a rapid metabolizer of drugs should prompt using maxi-

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Table 1. Antidepressant Drugs (1988–1996)

Fluoxetine (Prozac)
Bupropion (Wellbutrin)
Sertraline (Zoloft)
Paroxetine (Paxil)
Fluvoxamine (Luvox)
Venlafaxine (Effexor)
Nefazodone (Serzone)
Mirtazapine (Remeron)

mum doses of medication. In the United Kingdom, use of doses above those recommended is a common way of dealing with nonresponse. For some patients, longer trials may be necessary; this is particularly true for older patients.

An often overlooked contributing factor to treatment failure is patient use of recreational drugs or alcohol. The effects of alcohol and recreational drugs on the pharmacology of most psychotropic drugs are poorly understood, and it is best that patients be advised against their use during the initial phase of treatment. For example, cocaine inhibits dopamine and serotonin reuptake and may increase the rate of serotonin syndrome. Thus, it not only may obscure the actual effects or lack of effects of drugs, but can induce serious toxicity.

GENERAL STRATEGIES

When augmentation is used, one common approach is to combine two or more agents that are indicated for the same disorder (e.g., two antidepressants) but that either act on different neurotransmitter systems (e.g., serotonin and norepinephrine) or target different aspects of neurotransmission (e.g., reuptake transporters and receptors), or that combine these actions. Another approach is to combine two agents indicated for different disorders (e.g., an antidepressant and an antipsychotic).

An increasingly used approach employs an agent originally approved for the treatment of non-psychiatric disorders. Indeed, one of the more interesting aspects of the literature on antidepressant augmentation is that represented prominently among the agents are compounds not primarily identified as antidepressants. This is not to say they might not have antidepressant properties, but they have not been established in that respect. In fact, the use of drugs in ways and for disorders that are different from their original approved indications has gained acceptance in psychiatry. For example, drugs originally introduced as antidepressants are now used both alone and in combination with other drugs to treat anxiety disorders, schizophrenia, and obsessive-compulsive disorder. β -Adrenergic antagonists, once thought to cause depression, are now used to treat depression. Calcium channel blockers are used to treat mood disorders, and anticonvulsants are now first-line treatments for manic depressive illness. Thus, traditional boundaries between drugs no longer exist. Use is based on empirical observations that are then tested in open or con-

trolled trials, and attempts are then made to explain the observed results in terms of the known pharmacology of the drugs involved.

All of these strategies rely to some extent on combining drugs that target different neurotransmitter systems or different mechanisms involved in neurotransmission. Thus, augmentation may involve taking a broad-spectrum approach or enhancement of the activity of a particular neurotransmitter. For example, enhancing serotonin activity in the treatment of depression, obsessive-compulsive disorder, and schizophrenia is common practice. There are numerous agents that increase serotonin activity through different mechanisms. One danger when combining drugs that increase serotonergic activity is serotonin syndrome. One caveat concerning all antidepressants is that the actual reasons why drugs have antidepressant effects may be different from the neurotransmitter effects generally cited.

SPECIFIC COMBINATIONS: RELATIVE BENEFITS AND RISKS

In the absence of a well-established algorithm for augmentation strategies, each potential intervention needs to be considered in light of the clinical circumstances, which involve both the patient's clinical status and the benefits and risks associated with each add-on agent. The major theoretical advantage of using drug-combination strategies is that they result in unique pharmacologic mechanisms, ones that are not associated with conventional monotherapy with antidepressant agents. This supplement addresses the more common strategies: lithium, thyroid, bupropion, pindolol, anticonvulsant, dopamine agonist, stimulant, and antidepressant supplementation.

The major advantage of using drug-combination strategies is that they may work when sequential monotherapy has failed. Presumably, the combined effect of medications leads to a unique pharmacologic mechanism, one that is not associated with any single antidepressant agent. As noted by Thase and associates, another advantage to augmentation over switching is that it reduces the risk of a patient relapsing after discontinuation of the initial antidepressant. There are potential disadvantages of using multiple medications. These include (1) risk of adverse events, mainly due to drug interactions; (2) decreased patient compliance due to increased regimen complexity; (3) the limited available database on the comparative efficacy and safety of drug combinations, regardless of the strategy used (there are few double-blind trials, and the number of subjects studied tends to be comparatively small); (4) the potential for rare but serious adverse events; and (5) the absence of long-term treatment data.

Each of the interventions covered in this supplement is considered in terms of its potential efficacy, tolerability, safety, and convenience when used as treatment for unresponsive depressed patients.