Introduction

Pharmacologic Treatments of Major Depression: Are Two Mechanisms Really Better Than One?

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In the past 15 years, psychiatry has evolved rapidly, largely propelled by advances in the neurosciences and pharmacotherapy. As recently as the 1980s, the use of medications to treat depressive disorders was limited primarily to the most ill of patients. Today's antidepressants, however, treat a wide range of conditions with a spectrum of severity, and as such they have become one of the top-selling classes of medications. Treatment of depression, once the province of mental health professionals, is increasingly prescribed by primary care physicians, reflecting not only the increased awareness of the diagnosis but also the advent of safer, more tolerable, and easier-to-use antidepressants. Thus, many more patients are treated today than ever before. Indeed, the selective serotonin reuptake inhibitors (SSRIs) have created ripples in the popular culture that continue to this day. To suggest that the treatment of depression has become routine is scarcely an exaggeration.

Developing medications that are less toxic in overdose was a crucial first step in bringing treatment to a broader group of patients; molecules that also could minimize routine side effects helped swing the door open wider still. These developments also have facilitated the study and adoption of long-term maintenance treatment with antidepressants as a means of preventing recurrence.

The general direction of antidepressant drug development during this time has been toward increasing specificity. The SSRIs eclipsed tricyclic antidepressants (TCAs) as the treatment class of choice by targeting a single neurotransmitter system, thereby skirting issues of cardiac safety and anticholinergic side effects. The SSRI medications, too, have evolved toward greater specificity over time, with the most recently approved member of the class, escitalopram, demonstrating the highest selectivity for the serotonin transporter.[1] Increasing selectivity within the class of SSRIs has largely been regarded in a positive light; the narrower the pharmacologic profile of a given medication, the "cleaner" it is thought to be.

Although progress toward more specific medications over the years has generally yielded the benefit of enhanced tolerability, a similar trend has not been observed toward greater efficacy in depression. The SSRIs are no more effective than TCAs in the treatment of depression, and as yet none of the SSRIs has distinguished itself clearly as the best of the class. Moreover, the percentage of patients who do not respond to active medications in clinical trials typically continues to range from 20% to 50%. Still, SSRIs do appear to be potentially broader acting than TCAs, with effects in anxiety disorders, eating disorders, and dysthymia.

In recent years, interest has turned to medications that specifically target both the serotonin (5-HT) and the norepinephrine systems, the serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine and duloxetine). In a sense, this new focus represents a step away from the specificity or selectivity associated with SSRIs but still embraces some concept of selectivity, at least in comparison to TCAs, which also exert effects on other systems (e.g., histamine, acetylcholine). Results from early comparative trials, many of which are reviewed in this supplement, have been mixed: some indicated an incremental efficacy advantage for mixed-mechanism agents versus selected SSRIs, while others found no difference. Nevertheless, these findings lend a certain amount of support to the belief that, in the pharmacologic treatment of major depression, broader activity may be more beneficial than strict selectivity.

Where does the truth lie? This supplement attempts to examine a number of perspectives regarding the issue.

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The exploration begins with a look at evolving knowledge regarding the affinity and selectivity of antidepressants for various neurotransmitter receptors. In addition to underscoring the message that major depression is far more complex than our current understanding of neurotransmitter systems, the review reminds us that in vitro characterization of a compound does not always correlate with in vivo pharmacology.

We move on to an examination of the basic psychopharmacology of antidepressants, paying particular attention to the theoretical roles of 5-HT and norepinephrine in the pathology of depression. Animal models of depression are used to assess the effects of neurotransmitter depletion and help establish potential behavioral correlates for individual systems. How best to interpret such approaches is emphasized.

A review of the clinical psychopharmacology of antidepressants delves into the use of depletion studies in humans to characterize the interaction between therapeutic effect of specific drugs and activity of neurotransmitter systems. Findings underscore a heterogeneity of depressive disorders and suggest that altering monoamine function may be only one important part of addressing the neurobiology of depression.

Future efforts to accurately characterize the comparative merits of manipulating a single neurotransmitter system versus targeting two or more will require prospective trials in humans in which remission is the goal of treatment and adequate dosing of comparative compounds is ensured. Adequate duration of trial is also important, as is stratification for illness severity. Specific recommendations regarding design are offered.

Reviews of the literature on the relative efficacy and safety of various antidepressant classes, including specific agents, are also included. In addition to providing a perspective on the evolution of depression pharmacotherapy, these reviews analyze recent data in the context of whether two or more antidepressant mechanisms are better than one. There appears to be no simple answer to this essential question.

We return to considerations of clinical trial design, emphasizing an analysis of data on the use of response versus remission as the treatment goal. The application of these endpoints over the years is traced, affording a look at how trial design and practice have evolved along with our understanding of the disorder. Also considered is the concept of patient wellness as it relates to depression treatment, along with the various factors that promote or limit wellness. The use of more novel statistical methods (e.g., mixed-effects modeling) is also discussed.

The supplement concludes with a roundtable discussion covering 2 primary topics: whether current evidence provides us with any sense of whether 2 or more antidepressant mechanisms result in greater efficacy than does one and how prospective trials should be designed to help best answer this question.

Major depressive disorder remains a complex, heterogeneous condition, and the many advances in knowledge, theory, and treatment during the past half-century are overshadowed only by the great gaps that still exist in our understanding about the condition. Some believe that the next significant advances in treatment will occur not within the context of further neurotransmitter manipulation, but perhaps in other areas such as promoting neurogenesis. Also largely undefined are the influences of genetic factors on disease heredity, course, and treatment. Until a greater understanding is realized, however, it remains incumbent upon the field of psychiatry to strive for progressively better medications and treatment strategies. This supplement attempts to clarify the current status of commonly used medications.

REFERENCE

1. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–350