Unmet Need: What Justifies the Search for a New Antidepressant?

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The burden of major depressive disorder is huge, as is clearly documented by World Health Organization data. A major component of this burden is the episodic nature of depression. Depressive episodes may be precipitated by stress and if left untreated can become episodic, recurrent, and chronic. Hippocampal atrophy may be a consequence of chronic depression, but antidepressants and mood stabilizers have been suggested to prevent or reverse this damage. Adequate treatment is essential for preventing depression from becoming chronic. Unfortunately, current antidepressant treatments fall short of being adequate for many patients. Shortcomings such as low remission/high treatment-resistance rates, slow onset of action, side effects, and drug-drug interactions influence patient adherence, which may be as low as 56% after the first 3 months of treatment. Since many patients may need long-term antidepressant treatment, new antidepressants need to be developed that are effective, tolerable, and safe and that improve maintenance of wellness. *(J Clin Psychiatry 2002;63[suppl 2]:3–7)*

The growing burden of depression is evidenced by the projection that depression will be the second leading cause of disease or injury in the world by 2020.[1] While more than 40 antidepressants from different classes, with individual pharmacokinetic and/or pharmacodynamic effects, and with different mechanisms of action are available for the treatment of depression, only 30% to 40% of patients taking antidepressants achieve full remission.[2] Unless more effective antidepressants are developed, the burden of depression will only worsen, thereby justifying the search for new antidepressants.

THE BURDEN OF MAJOR DEPRESSIVE DISORDER

Epidemiology

Major depressive disorder is widely prevalent. The lifetime risk for the disorder is 12.7% for men and 21.3% for women,[3] meaning that at any given time an estimated 340 million people worldwide and 18 million people in the United States have major depressive disorder.[2] Further, the World Health Organization (WHO) estimates that unipolar depression accounts for 11% of all disability, and, according to projections, disability from depression will continue to worsen in the next 20 years.[1] Disability is classified by the WHO as any restriction or loss of ability to perform an activity due to impairment.[1] A recent study by Kessler et al.[4] analyzed data from 2 national surveys and found that depressed workers had 1.5 to 3.2 more disability days in a 30-day period than other workers, which resulted in a salary-equivalent productivity loss averaging between $182 and $395. In addition to having higher disability than nondepressed people, depressed people have higher mortality and health care costs 2 to 3 times higher, not including mental health care costs, when compared with nondepressed people. A survey[5] of 78,463 adults in 6 European countries found that people suffering from major depression made almost 3 times as many visits to their general practitioner or family doctor as people not suffering from depression. The increased risk for people with depression having other medical diseases may be conceptualized by this rule of thumb: 20% of all patients use 80% of health care resources, and 33% of costs are linked with treatment of psychiatric problems, with the largest contribution being depression. Increased comorbid illnesses, health care costs, mortality, disability, and widespread prevalence all are major contributors to the burden of major depression.

Further heightening the impact is the onset of symptoms of the disorder at an early age. Although the mean age at diagnosed onset is 21 years for bipolar disorder and 27 years for major depressive disorder—and often later in naturalistic settings—the age at onset for symptoms of these disorders ranges from 15 to 19 years.[6] A study by Pine et al.[7] examined the longitudinal associations between adolescent and adult anxiety and depressive dis-

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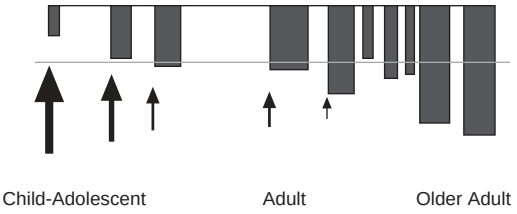
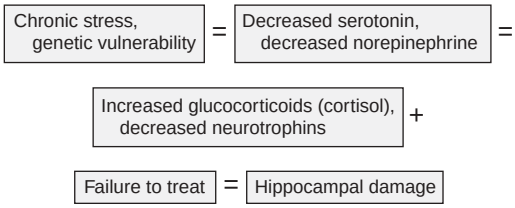
Figure 1. Influence of Stress on the Lifetime Course of Untreated Depression[a]



[a]Adapted with permission from Greden.[8] Shaded boxes designate depressive episodes. Line indicates depressive episodes that meet the criteria for major depressive disorder. Arrows designate stressors. Size of arrows and boxes signifies estimates of severity.

Figure 2. Chronic Stress Results in Hippocampal Damage



orders. Using structured interviews, researchers gave a sample of 776 young people DSM-based psychiatric assessments in 1983, 1985, and 1992. The results of the study showed an approximately 2- to 3-fold increased risk for adulthood anxiety or depressive disorders in subjects who had anxiety or depressive disorders in adolescence. Unfortunately, symptoms of major depression in teenagers are often completely ignored or attributed to substance abuse, attention-deficit/hyperactivity disorder, or an adolescent adjustment disorder. When depression is not recognized or treated successfully, the chances of its becoming recurrent and episodic increase, and the cascade of burden begins.

Stress and Hippocampal Atrophy

Genetic vulnerability and stressors also interact to influence depression's untreated lifetime course. Eventually, researchers and clinicians anticipate being able to predict who is most vulnerable to depression, which will aid in preventing major depressive disorder from becoming chronic and treatment resistant. In the meantime, effective strategies for preventing a chronic state are antidepressant treatment coupled with cognitive-behavioral and/or interpersonal therapy.[2] Unfortunately, depression often recurs when antidepressants are stopped after treatment of an episode. Since episodes may be triggered in vulnerable people by a stressful life event such as loss of a loved one, financial upheaval, or trauma, and these are virtually impossible to avoid, the pattern may become recurrent if no continued antidepressant treatment is in place. Over time a person's sensitivity to stressful events increases so that eventually even minor stressors can lead to severe depressive episodes. Thus, a cycle of stress and depression ensues, with the number of depressive episodes getting closer together and becoming more severe as their number increases (Figure 1).[8]

When left untreated, chronic stress and the subsequent depression may cause neuronal degeneration via glucocorticoid (the adrenal steroids secreted during stress) excess and/or alterations in neurotrophins (Figure 2). Serotonergic and adrenergic alterations may play key roles in this cascade. Although much remains to be learned, the net result seems to be hippocampal damage.[9] When rodents are exposed to levels of glucocorticoids usually experienced during weeks or months of major stress, the rodents' hippocampal CA3 neurons atrophy and memory loss occurs.[10] Sheline et al.,[9] to evaluate the possible impact in humans with depression, conducted a study that evaluated hippocampal volume in older women with recurrent major depression. The subjects in the study ranged from 51 to 86 years of age. Although all subjects had experienced recurrent major depression, none were depressed at the time of the study and none had any known medical comorbidity. (By excluding subjects with histories of alcohol and substance abuse as well as those with vascular problems, the authors sought to avoid other factors that may affect brain volume.) The hippocampal volumes of the subjects were compared with those of normal controls by using volumetric magnetic resonance imaging. The findings of the study were that subjects with a history of recurrent major depression had smaller hippocampal gray matter volumes than normal controls. Total cerebral volumes did not differ between the groups. Since none of the subjects were depressed at the time of the study, Sheline et al. hypothesized that the smaller hippocampal volumes were probably not the result of acute effects of corticosteroids but rather of the chronic depressive episodes (Table 1).[9] The authors concluded that the severe morbidity of depression might be relieved by neuroprotective approaches aimed at preventing depression and reducing hippocampal damage.

Fortunately, hippocampal damage does not have to be permanent because neuronal atrophy may be reversible. Young et al.[11] reported that an enriched environment can stimulate neurogenesis as well as reduce spontaneous apoptotic cell death in the rat hippocampus by 45%. Further, the expression of brain-derived neurotrophic factor (BDNF) and the phosphorylation of the transcription factor cyclic-AMP response element binding protein (CREB) are increased by an enriched environment.[11] Neurogenesis appears to be enhanced and neurogenesis degeneration reversed by antidepressants and mood stabilizers, probably via alteration of cyclic-AMP, CREB, BDNF, and other neurotrophic factors.

Table 1. Hippocampal Volumes and Clinical Data for Depressed Patients[a]

Subject Number	Left Hippocampal Volume (mm^3)	Right Hippocampal Volume (mm^3)	Time Spent Depressed (days)	Time Since Depression (months)
02	2049	2233	252	10
03	2237	2637	196	24
04	1690	1851	2065	8
09	1897	2109	3752	10
10	1842	1977	3276	36
11	2081	2021	210	6
13	2265	2269	2160	6
14	2485	2301	21	524
15	2407	2536	980	36
18	2632	2894	119	168

[a]Data from Sheline et al.[9]

A recent study by Malberg et al.[12] investigated the effect of antidepressants on hippocampal neurogenesis in adult rats. Thymidine analog bromodeoxyuridine (BrdU) was used to mark dividing cells. The results of the study showed that chronic, but not acute, antidepressant treatment significantly increased the number of BrdU-labeled cells in the dentate gyrus and hilus of the hippocampus. Different classes of antidepressant and nonantidepressant agents were given to the rats, but only the antidepressant agents increased the number of cells. Thus, antidepressant treatment may reverse stress-induced atrophy through neurogenesis, which may be related to the therapeutic action of antidepressants.[12] Lithium has also been shown to induce hippocampal neurogenesis.[13] Quantitative 3-dimensional magnetic resonance imaging studies revealed that chronic lithium treatment significantly increases total gray matter volume in patients with manic-depressive illness. Finally, a review by Duman et al.[14] discussed the intracellular mechanisms believed to underlie the effects of antidepressant treatments on hippocampal neurons. It is hypothesized that CREB and BDNF are enhanced by chronic antidepressant treatment, thus protecting neurons from any future damage as well as reversing previous damage and atrophy. While details are emerging, more studies are needed to test this hypothesis.

THE SHORTCOMINGS OF AVAILABLE ANTIDEPRESSANTS

Remission and Treatment Resistance

The current group of antidepressants, such as selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and reversible inhibitors of monoamine oxidase, are much improved and safer than earlier antidepressants like monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Despite improvements, these newer agents still have numerous shortcomings, the most notable of which may be low remission/high treatment-resistance rates and low adherence rates. Approximately 30% of people with depression do not respond to antidepressant treatment, but only an estimated 70% of patients who do respond to antidepressant treatment actually remit.[2] These percentages indicate that treatment resistance may be the norm when complete remission is used as the determinant for successful treatment.[2] Since remission is the target of treatment for depression, antidepressant agents are not adequately meeting the treatment goal.

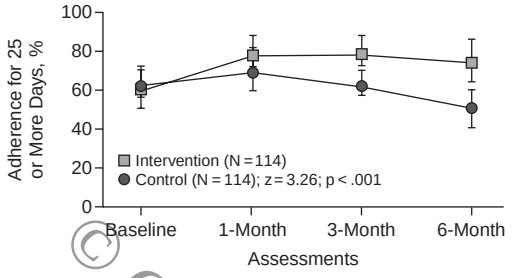
Onset of Action, Side Effects, and Drug-Drug Interactions

Other problems with the currently available antidepressants include delayed onset of action, side effects, and drug-drug interactions. The onset of action for antidepressants is delayed from 2 to 12 weeks,[15] which may cause some patients to prematurely believe the treatment is ineffective because their symptoms have not been relieved. Compounding the problem of delayed onset is the appearance of side effects soon after the start of treatment.[15] Although the newer antidepressants have side effect profiles that are more tolerable than those of MAOIs and TCAs, the side effects of newer agents still cause some patients enough discomfort to affect compliance. Drug-drug interactions may be a problem for patients taking antidepressants because most of the agents are metabolized by the cytochrome P450 system of enzymes. Up to 30% of patients may be prescribed an antidepressant that interacts with cytochrome P450 enzymes simultaneously affected by another concomitant medication.[16]

Patient Adherence

Many of the aforementioned shortcomings of antidepressants contribute to low patient adherence to treatment. As many as 44% of patients stop taking their prescribed antidepressant after 3 months of treatment.[17] Crucial to treatment adherence is that patients perceive they are receiving some benefit from continuing to take the medication,[16] and educating patients about antidepressant treatment may be one way to help them understand that benefit. Katon et al.[18] found that patients who were part of a collaborative care intervention had better adherence to antidepressant treatment than patients who were receiving usual treatment by a primary care physician (Figure 3). The collaborative care approach educates patients and integrates mental health professionals into the primary care setting to help primary care physicians provide guideline-based treatment.[18] In the study,[18] a total of 228 patients, who had been diagnosed as depressed and were being treated with antidepressant medication, were randomly assigned to collaborative care intervention (N = 114) or usual care (N = 114). The patients in the collaborative care intervention received education and frequent visits from a psychiatrist working with the primary care physician to improve pharmacologic treatment. Follow-up assessments for both groups were made at 1, 3, and 6 months via a tele-

Figure 3. Adherence to Antidepressant Treatment for Intervention Patients vs. Usual Care Patients[a]



[a]Reprinted with permission from Katon et al.[18] Adherence is for 25 or more days of the last 30 at baseline and at 1, 3, and 6 months. Error bars indicate 95% confidence intervals.

phone survey team. Patients receiving the collaborative care were more likely to have recovered from their depression at 3 and 6 months than the patients receiving usual care. Improving patient adherence through interventions is possible, as this study demonstrates. Other interventions to improve compliance include the Medication Event Monitoring System caps that record when the pill container is opened and tailored messages on personal digital assistants that remind patients to take their medication. Interactive voice recognition rating scales, which are discussed in this supplement by John H. Greist, M.D.,[19] are completed by patients who are then contacted by physicians if symptoms worsen or reoccur.

Developing Effective Antidepressants

Given the longitudinal, recurrent pattern of major depressive disorder, antidepressant treatment may have to be long term for many patients. Studies on continuation and maintenance antidepressant therapy show that antidepressants are more effective than placebo in preventing relapse and recurrence of depression.[20] (Treatment is most effective when antidepressants are administered at their full dose.) One strategy for preventing relapse is treating patients who have had 3 episodes of depression with extended antidepressant maintenance.[8] However, for this strategy to be most effective, several aspects of treating and diagnosing depression may need to be changed. First, new antidepressants need to be developed. These new agents may be dual or triple reuptake inhibitors developed on the basis of the biogenic-amine mechanism, or the new agents could be developed from completely different mechanisms of actions. (See the article by Phil Skolnick, Ph.D.,[21] in this supplement on new mechanisms of action for antidepressants.) The new antidepressants also need to be effective, tolerable, and safe for those patients that may need long-term treatment. Second, new measurement tools for diagnosing and assessing depression are needed so antidepressant treatment can be better tailored to individual patients' needs. Finally, the paradigm for assessing new antidepressant candidates needs to be changed so that proper emphasis is given to longer-term maintenance of wellness.

CONCLUSION

The search for new antidepressants is justified by the inability of current antidepressants to provide adequate treatment and maintenance of wellness to all patients suffering from depression. Many of the available antidepressants have low remission/high treatment-resistant rates, slow onset of action, side effects, and drug-drug interactions, all of which influence patient adherence. Because depression left untreated tends to become chronic, low patient adherence to treatment may contribute to the burden of depression. Further, evidence shows that chronic depression causes hippocampal atrophy, but antidepressants can reverse this damage. Therefore, antidepressant agents that are more effective, more tolerable, and safer than current agents, especially in the long term, need to be the goal of future antidepressant development.

REFERENCES

1. Murray CJL, Lopez AD, eds. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability From Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, Mass: Harvard University Press; 1996
2. Greden JF. The burden of disease for treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):26–31
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:8–19
4. Kessler RC, Birnbaum BC, Frank RG, et al. Depression in the workplace: effects on short-term disability. Health Aff 1999;18:163–171
5. Lepine JP, Gastpar M, Mendlewicz J, et al. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 1997;12:19–29
6. Roy-Byrne P, Post RM, Uhde TW, et al. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 1985;317:1–34
7. Pine DS, Cohen P, Gurley D, et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry 1998;55:56–64
8. Greden JF. Recurrent depression: its overwhelming burden. In: Greden JF, ed. Treatment of Recurrent Depression. Washington, DC: American Psychiatric Publishing Inc; 2001:1–18
9. Sheline YI, Wang PO, Gado MH, et al. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996;93:3908–3913
10. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–935
11. Young D, Lawlor PA, Leone P, et al. Environment enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med 1999;5:448–453
12. Malberg JE, Eisch AJ, Nestler EJ, et al. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20: 9104–9110
13. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 2000;48: 740–754
14. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 1999;46:1181–1191
15. Culpepper L. Early onset of antidepressant action: impact on primary care.

J Clin Psychiatry 2001;62(suppl 4):4–6
16. DeVane CL. Pharmacologic characteristics of ideal antidepressants in the 21st century. J Clin Psychiatry 2000;61(suppl 11):4–8
17. Lin EHB, Van Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995;33 (1):67–74
18. Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression. Arch Gen Psychiatry 1999;56:1109–1115
19. Greist JH, Mundt JC, Kobak K. Factors contributing to failed trials of new agents: can technology prevent some problems? J Clin Psychiatry 2002;63 (suppl 2):8–13
20. Nierenberg AA, Alpert JE. Depressive breakthrough. Psychiatr Clin North Am 2000;23:731–742
21. Skolnick P. Beyond monoamine-based therapies: clues to new approaches. J Clin Psychiatry 2002;63(suppl 2):19–23