WARF has been accused of "stifling" the market for stem cells, particularly for academic researchers. It has responded, in essence, that because Thomson's research was privately funded, WARF is being generous to share at all.[3] But this argument fails to recognize that most universities continually strive to ensure that corporate funding does not conflict with their academic mission, of which the wide dissemination of knowledge is surely a part.

WARF has also argued that it was "learning" how to establish appropriate market conditions, having repeatedly tried to reshape the stem-cell market by changing its contractual terms, partly in response to objections from the scientific community.[4] In January 2007, for example, WARF began to permit industry-sponsored research involving its stem cells to be pursued at academic institutions without a license, and it eased restrictions on stem-cell transfers among researchers. It has gradually loosened its control, simplified its practices, and reduced its prices. Such evolution makes it clear that it is not the patents themselves but the contracts through which patent rights are imposed that can impede the advancement of science. If replicated elsewhere, restrictive practices could balkanize research, causing experimental designs and collaborations to be driven by legal rather than scientific choices.

By contrast, one can envision an open commons for human embryonic stem-cell research, combined with strong incentives for commercial research investments. Such a scheme would not mean eschewing patent rights. Rather, it would require a commitment by academic institutions to allow a wide-reaching reciprocal exemption for the free exchange of materials for research purposes, with relevant stipulations built into commercial licenses. These terms could be extended to for-profit researchers while they conducted research, with an agreement to negotiate effective commercial terms if and when products were identified. At the same time, federal agencies could expand their investments in institutions that facilitate the rapid exchange, validation, and comparative analysis of stem cells as envisioned by the International Society for Stem Cell Research. Such a scenario would be in the long-term best interests of science.

The challenge for universities today is not so much to choose whether or not to patent their ideas, but rather to determine how best to control their discoveries and whether their technology-transfer policies advance their broader mission.

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Expanding the Black Box — Depression, Antidepressants, and the Risk of Suicide

Richard A. Friedman, M.D., and Andrew C. Leon, Ph.D.

On May 2, 2007, the Food and Drug Administration (FDA) ordered that all antidepressant medications carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults 18 to 24 years of age. Since October 2004, antidepressants have been required to have a black-box warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior in children and adolescents.

The new warning also states that there is no evidence of an increased risk for adults older than 24 years of age and that the risk is actually decreased for adults 65 years of age or older. Strikingly, the label states that "depression and other serious psychiatric disorders are themselves associated with increases in the risk of suicide," which makes it the first black-box warning to note that a disease itself carries risk — and implies that there is risk in not using the very medication being warned about.

The new warning was developed in the wake of a December 2006 meeting of the FDA's Psychopharmacologic Drugs Advisory Committee, which focused on the

controversial link between antidepressants and suicide risk in adults. During an often contentious public session, the advisory committee heard from psychiatric experts and from aggrieved family members, who sometimes expressed outrage at the FDA when they spoke of the death of loved ones who had taken antidepressants. In the end, the committee voted 6 to 2 in favor of extending the black-box warning to include adults 18 to 24 years of age.

The notion that antidepressants might be associated with an increased risk of suicidality (suicidal ideation, behavior, or both) in some patients is hardly new. Clinicians have known for years that during the first few weeks of treatment with antidepressants, some patients become "activated" — energized and agitated — before their depressed mood lifts, and that combination makes them more likely to act on preexisting suicidal impulses. But because suicidal thinking, feeling, and behavior are core symptoms of depression, there is no way to know whether suicidal symptoms that develop during treatment are due to the underlying illness or the medication.

The FDA used the best available data in attempting to disentangle the effects of treatment from those of illness by comparing the rates of suicidal symptoms among patients taking antidepressants with rates among those taking placebo. The advisory committee considered the results of comprehensive meta-analyses of an enormous data set: data on 99,839 participants who had enrolled in 372 randomized clinical trials of antidepressants conducted by 12 pharmaceutical companies during the past two decades.

The primary analyses were restricted to participants in trials for psychiatric disorders. There were 8 suicide deaths: in 5 of 39,729 participants assigned to the investigational drug, 2 of 27,164 assigned to placebo, and 1 of 10,489 assigned to an active comparator. In addition, 501 participants had suicidal feelings or thoughts or nonfatal suicide attempts — 243 while receiving an investigational drug, 194 while receiving placebo, and 64 while receiving an active comparator. No increased risk of suicidal behavior or ideation was perceptible when analyses were pooled across all adult age groups. In age-stratified analyses, however, the risk for patients 18 to 24 years of age was elevated, albeit not significantly (odds ratio, 1.55; 95% confidence interval, 0.91 to 2.70).

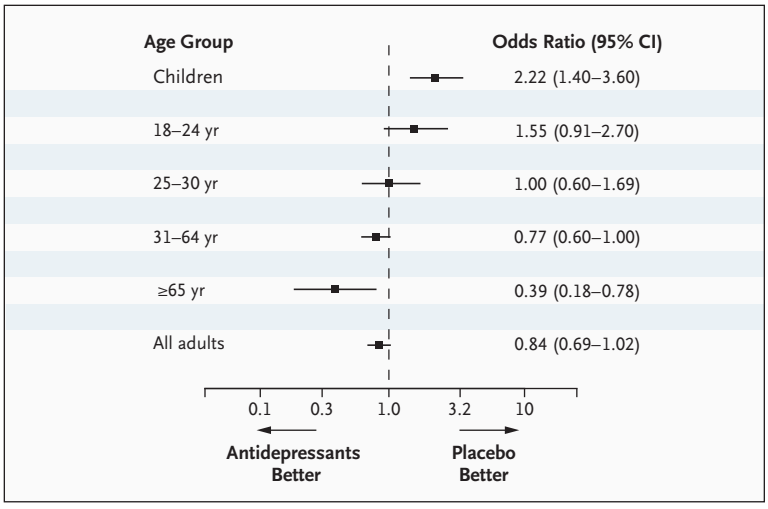
Why, then, did the committee recommend expanding the black-box warning to include this age group? First, the threshold for threat to safety is generally lower than that for efficacy, and the data did not provide strong evidence of an absence of risk. Second, and most important, the trend across age groups toward an association between antidepressants and suicidality (see chart) was convincing, particularly when superimposed on earlier analyses of data on adolescents from randomized, controlled trials.[1]

These new meta-analyses had other key strengths: the data set was vastly larger than any previously assembled to study suicidality or interventions for a psychiatric disorder, and the results of independent analyses by two groups of FDA reviewers using different statistical methods were virtually identical.

Yet the data come from studies designed primarily to assess short-term efficacy, not long-term safety, which is of critical importance. In fact, the suicidal symptoms highlighted in the analyses came from adverse-event reports, not prospectively collected data obtained with the use of depression-rating scales. And adverse-event reports are subject to ascertainment bias. For instance, participants who report common side effects of antidepressant treatment, such as sexual dysfunction, would be more likely to be asked about other adverse effects and perhaps more likely to report suicidal symptoms than would subjects taking placebo. Similarly, a patient in a blinded trial who took an overdose of an antidepressant would be more likely than one who took an overdose of placebo to present at an emergency room, triggering an adverse-event report. Furthermore, younger participants might conceivably be more likely than older participants to report adverse events. And the meta-analyses ignored attrition, which might have varied with age.

But it is confounding by indication that poses the greatest difficulty for interpretation: Is suicidality caused by the disease or the treatment? The data do provide a hint. More than 20% of the data came from 43 studies of treatment for nonpsychiatric indications (e.g., obesity, smoking cessation, and insomnia) and 34 trials for nonbehavioral indications (e.g., fibromyalgia, diabetic neuropathy, and stress urinary incontinence), but these data were not included in the primary analyses. The risk per person-year of treatment was substantially lower in trials for nonpsychiatric indications, suggesting that depression played a key role in suicidality and that antidepressants do not themselves generate new suicidal symptoms.

Many other potentially useful



Odds Ratios for Suicidal Behavior and Ideation among Patients Treated with Antidepressants for Psychiatric Indications, as Compared with Placebo.

Data are from the Summary Comments of the December 13, 2006, meeting of the FDA's Psychopharmacologic Drugs Advisory Committee. CI denotes confidence interval.

analyses were not conducted, primarily because the requisite data were not among those requested by the FDA. For instance, it is generally believed that the risk of suicidality associated with treatment emerges early on, perhaps during the first 2 weeks of therapy, yet information on the timing of events was not available. Furthermore, the most persuasive feature of the data on adolescents that were presented to the advisory committee in 2005 was that only 3 of 15 randomized, controlled trials involving patients with major depression showed efficacy of antidepressants. The risk–benefit ratio in individual trials in adults was not examined in the current meta-analyses; instead, one aggregated pair of approximate response rates was presented: 50% response to active treatment and 40% to placebo. Without efficacy data, not even the most superficial risk–benefit estimate could be calculated.

The new black-box warning is clearly an attempt to balance the small risk posed by antidepressants against their well-documented benefits. But this new label has the potential to confuse both patients and physicians. After all, if depression and other psychiatric illnesses are "associated with increases in the risk of suicide," as the warning states, and antidepressants are known to be effective treatments for such disorders, why not just state the obvious: that untreated depression and psychiatric illness carry a significant risk? Because such a statement would too closely resemble a treatment recommendation, which is outside the purview of the FDA.

Whether the new warning will do more good than harm is not clear. There are already some signs that the warning will discourage depressed patients and their families from seeking treatment and frighten physicians away from prescribing antidepressants. After the FDA mandated the first black box in October 2004, a survey found that rates of prescriptions for antidepressants for children and adolescents were 18% lower in July 2004 than they had been in July 2003.[2] And for the first time in more than a decade, the Centers for Disease Control and Prevention reported a slight increase in the suicide rate among teenagers in 2004. It is too early to know whether this is a random fluctuation or the start of a real increase, but there are consistent ecologic data linking the decrease in the adolescent suicide rate during the past decade with the steady increase in the use of antidepressants in this population.[3] Moreover, in a study of adolescents who had committed suicide in New York City during a 10-year period, antidepressants were very rarely detected in postmortem studies.[4]

There may be controversy about the risk posed by antidepressants, but there is none about the risk associated with untreated depression: estimates of the lifetime risk of suicide in depressed persons range from 2.2 to 15%, depending on the population under study — not to mention the considerable suffering and functional impairment caused by this illness.[5] In contrast, the FDA meta-analyses reveal an absolute risk of suicide in patients taking investigational antidepressants of 0.01%. Granted, this rate reflects risk during the short duration of a randomized trial, typically 4 to 12 weeks, but suicide is clearly an extremely rare treatment-emergent phenomenon.

How should physicians deal with the new black-box warning? The real killer in this story is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease. Still, clinicians need to tell their depressed patients that some people who take antidepressants have an increase in suicidal symptoms, especially early in treatment, and they need to follow their patients very closely during the first 4 to 6 weeks of treatment.

An interview with Dr. Leon can be heard at www.nejm.org.

Dr. Leon reports receiving consulting and lecture fees from Pfizer and Eli Lilly. No other potential conflict of interest relevant to this article was reported.

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FOCUS ON RESEARCH

Discovery of New Infectious Diseases — Bartonella Species

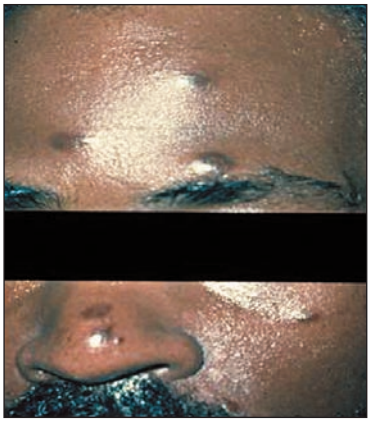
Gary P. Wormser, M.D.

Related article, page 2381

Careful microbiologic evaluation of patients with various illnesses has led to the discovery of many important pathogens in recent decades, including human immunodeficiency virus (HIV), legionella species, *Borrelia burgdorferi* (the agent of Lyme disease), human herpesvirus 8 (HHV-8), and numerous others. Success in these endeavors, however, was critically dependent on the availability of the appropriate technology for both the detection of the microorganism and its characterization to the level necessary to permit clear differentiation from already recognized pathogens. The delay between the recognition of a particular clinical syndrome and the identification of its causative agent has been highly variable. Whereas HIV, for example, was discovered within 2 to 3 years after the recognition of AIDS, it took more than 120 years to establish that HHV-8 was the cause of Kaposi's sarcoma.

Bartonella are small, curved, pleomorphic, gram-negative rods. A characteristic feature of these bacteria is their adherence to and invasion of erythrocytes, although this phenomenon is dependent on the erythrocytes' species of origin. A unique facet of infection with bartonella is the ability of these microorganisms to stimulate neovascular proliferation in tissues, presumably by causing endothelial-cell proliferation and migration. Although highly fastidious, bartonella are often cultivable, and available methods for analyzing the genetic and protein compositions of the isolated microorganism permit very precise molecular characterization. Having used such an approach, Eremeeva et al. present compelling evidence in this issue of the *Journal* (pages 2381–2387) that a new bartonella species, *Bartonella rochalimae* sp. nov., should be added to the list of recognized human pathogens.

Of the 19 recognized and extant species and subspecies in the expanding bartonella genus before the report by Eremeeva et al., perhaps 9 had been linked to human infections, but only 3 of them had been implicated in such infections frequently. The spectrum of clinical illness varies with the species causing the infection, but even among patients infected with the same species, the clinical features can be surprisingly variable. At times, the clinical illness caused by these microorganisms is so distinctive that bartonella infection would be at or near the top of the differential diagnosis, whereas in other patients the presentation is completely nonspecific.



Bacillary Angiomatosis.

Courtesy of Dr. Alvin E. Friedman-Kien.

B. henselae is now regarded as the principal cause of cat scratch disease, the most frequently recognized bartonella infection in humans. The cause of cat scratch disease was not conclusively elucidated until more than 40 years after its recognition as a clinical entity in 1950. The hallmark of this infection is the prominent enlargement of lymph nodes that drain lymph from cutaneous sites where *B. henselae* was introduced by the