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Recent Regulatory Changes in Antidepressant Labels:

Implications of Activation (Stimulation) for Clinical Practice

Peter R. Breggin, MD

ABSTRACT

Recent attention has been given to the risk of suicidality associated with antidepressants. More focus is needed on the risk of activation or stimulation as described in the new class warnings from the Food and Drug Administration, including anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, and other unusual changes in behavior, worsening of depression, and suicidal ideation. The medications most commonly associated with activation are the selective serotonin reuptake inhibitors as well as bupropion and venlafaxine. It is important for physicians to identify these relatively common adverse drug reactions as early as possible and to respond when necessary by reducing the dose or withdrawing the medication on a safe schedule. Careful monitoring and patient education can help to prevent activation with the potential for harm to self or others.

INTRODUCTION

Recent United States Food and Drug Administration-mandated class warnings concerning the increased risk of suicidality in children treated with antidepressants have drawn a great deal of attention. More recently, the FDA has announced that it is investigating growing concerns about antidepressant-induced suicidality in adults.[1]

Almost no attention has been given to a far broader concern within the FDA about the "activating" effects of these medications in children and adults. On March 22, 2004 the FDA issued a Public Health Advisory in regard to children and adults in which it stated:

> *The agency is also advising that these patients be observed for certain behaviors that are **known** to be associated with these drugs, such as, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania. (emphases added)*[2]

Needs Assessment: The subject of antidepressant-induced adverse reactions, particularly suicidality, is currently a topic of great current interest and controversy. The Food and Drug Administration has issued warnings about suicidality in children and is investigating suicidality in adults. However, the FDA's deliberations and warnings have also focused on a much more common and potentially dangerous activation or stimulation syndrome. Many practitioners are insufficiently aware of this syndrome and the FDA's recent warnings about it. Physician awareness and patient education are the keys to preventing harm to self or others during an antidepressant-induced activation or stimulant syndrome.

Learning Objectives:

- Recognize the activation syndrome associated with antidepressants.
- Respond to potential signs of danger to self or others.
- Identify those drugs most likely to cause activation.

Target Audience: Primary care physicians and psychiatrists.

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Dr. Breggin is founder and director emeritus of the International Center for the Study of Psychiatry and Psychology, and has a private practice in Ithaca, New York.

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Please direct all correspondence to: Peter R. Breggin, MD, 101 East State St, No. 112, Ithaca, NY 14850; Tel: 607-272-5328; Fax: 607-272-5329; Web site: www.breggin.com.

The final version of the class label was approved by the FDA on January 26, 2005 and is now required for all antidepressants.[3] Beneath the black-box warning with the heading "Suicidality in Children and Adolescents," there is an additional lengthy warning section. The first headline beneath the black box reads, "WARNINGS—Clinical Worsening and Suicide Risk." Without specifically naming it, this section contains a warning about the activation syndrome:

> *The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.*[3]

The label warning specifically refers to children and adults. By indicating that nonpsychiatric patients can develop these reactions, the FDA class label challenges the commonly held belief that only patients with a bipolar history or vulnerability are at risk for developing antidepressant overstimulation.

A section of the label devoted to information for patients and their families repeats the warning about activation and elaborates on the warning in regard to clinical worsening and suicide risk:

Patients, their families and caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, and other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.[3]

THE ACTIVATION OR STIMULATION SYNDROME

Most of the symptoms described by the FDA are the result of activation or stimulation causing a syndrome similar to that encountered with classical stimulants such as amphetamine, methamphetamine and methylphenidate, especially in high doses.

Physicians and patients need to be alert to the activating properties of the newer antidepressants. Compared to antidepressant-induced suicidality, activation is bolstered by a much larger scientific literature and poses a far more common risk.[4] Activation has the potential for equally disastrous outcomes and should be the first consideration whenever a patient's condition begins to worsen while taking antidepressants. If the physician mistakenly identifies these adverse drug reactions as a part of the patient's original psychiatric disorder, he or she may continue or even increase the antidepressant dose in the hope of controlling the activation. This can lead to severe cases of mania and psychosis.

Eventually, the FDA decided to apply the new label changes to all 34 antidepressants on the market, including older, more sedating antidepressants such as amoxapine, trazodone HCl, amitriptyline, doxepin, and imipramine. However, the FDA actually studied and originally focused on the newer antidepressants. The "drugs under review" at that time, according to the March 22, 2004 FDA Talk Paper,[2] were bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine. These were the drugs most often cited by the public at the two FDA hearings.

THE NEW FDA MEDICATION GUIDE

The FDA now requires that the families of children receiving antidepressants received a booklet entitled *Medication Guide: About Using Antidepressants in Children and Teenagers.*[5] These observations are aimed at children and adolescents rather than children and adults. Its third point is entitled "You Should Watch for Certain Signs if Your Child is Taking an Antidepressant." It states, "Contact your child's healthcare provider right away if your child exhibits any of the following signs for the first time, or if they seem worse, worry you, your children, or your child's teacher." It lists the following danger signs: thoughts about suicide or dying; attempts to commit suicide; new or worse depression; new or worse anxiety; feeling very agitated or restless; panic attacks; difficulty sleeping (insomnia); new or worse irritability; acting aggressive, being angry, or violent; acting on dangerous impulses; an extreme increase in activity and talking; an other unusual changes in behavior or mood.[5]

The medication guide does not specify a causal link between these reactions and the medications, but clearly implies that these reactions are associated with medication.[5] The entire list is consistent with the activation or stimulation syndrome. The inclusion of anger, aggression, and violence indicates a concern that antidepressant reactions can pose a danger to others.

Canadian and British Regulatory Warnings

Canada also changed its warnings in regard to antidepressants. On June 3, 2004, before the US FDA issued its formal label changes, Health Canada (the Canadian drug regulatory agency) issued an advisory: "Health Canada advises Canadians of stronger warnings for selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants."[6] The Canadian advisory made a broader warning than the later United States version, that "these new warnings indicate that patients of all ages taking these drugs may experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others." Unlike the FDA, Health Canada applied the warning to children and adults in regard to suicidality. It also warned about both harm to self and to others (violence):

> *Patients, their families and caregivers should note that a small number of patients taking drugs of this type may feel worse instead of better, particularly within the first few weeks of treatment or when doses are adjusted. For example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts that could involve self-harm or harm to others. (emphases added)*[6]

In Great Britian all SSRIs, except fluoxetine, have been banned for the use of treating depression in children. The main concern surrounded increased suicidality that was associated with SSRIs including fluoxetine.[7,8]

DISCUSSION

Early reports of an SSRI-induced stimulant syndrome began appearing more than a decade ago[9] and a detailed review has been recently published.[4] Sufficient clinical and research evidence has now accumulated for the FDA to require a label warning that describes this activation or stimulation syndrome. The syndrome closely mimics the adverse reaction profile physicians usually associate with the classical stimulants. The syndrome represents a continuum of effects that can present in mild forms (eg, minimal insomnia, anxiety, or irritability) as well as more severe forms (violence and mania). Clinical experience suggests that continued exposure to the drug can lead to a worsening of the patient's reaction.

The syndrome includes akathisia, a combination of internal dysphoria or subjective discomfort with a need to move about for relief. Patients may describe seemingly bizarre feelings as "electrical impulses down my nerves," "shocks in my body," "skin crawling," or "trembling and pulsing inside my body." In some cases, the patient may not manifest overt signs of hyperactivity.[10] Severe akathisia can be associated with a marked deterioration in the patient's condition, suicidality, and violence.[10,11]

When a patient is taking medications that can induce akathisia, such as antidepressants and neuroleptics, a physician must take great care not to dismiss the patient's seemingly bizarre reports as symptoms of a mental disorder. Otherwise, the physician is likely to increase the medication dose when a reduction or discontinuation is required to relieve the patient's discomfort.

Mania is the extreme manifestation of drug-induced activation. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision (*DSM-IV-TR*),[10] manic episode and bipolar disorder should not be diagnosed when the episode first occurs during medication treatment with antidepressants. For example, in the *DSM-IV-TR* at the bottom of the table for "Criteria for Manic Episode," it states in a note: "Manic-like episodes that are clearly caused by somatic antidepressant treatment... should not count toward a diagnosis of bipolar disorder." The correct diagnosis in most of these cases is substance-induced mood disorder with manic features. Yet, these patients are often mistakenly diagnosed with bipolar disorder. These patients may be told that the medication has unmasked a pre-existing underlying manic disorder. While this may be true at times, there is no way to know with certainty, especially in cases where there is no prior history of mania. In addition, these patients may be given mood stabilizers or neuroleptics when they really need discontinuation of the offending antidepressant.

The rates for antidepressant-induced mania in patients taking SSRIs are much higher than many clinicians may realize. Henry and colleagues[12] observed 44 antidepressant-treated bipolar patients for at least 6 weeks and found that switches to hypomania or mania occurred in 27% of all patients and 24% of the subgroup treated with SSRIs.

Most studies produce lower rates in the range of approximately 8% to 9% for SSRI-induced hypomania and mania across varying durations and conditions of exposure.[13] Morishita and Arita[13] carried out a retrospective review of 79 paroxetine-treated patients in a psychiatric clinic. One patient became manic and seven became hypomanic for a combined prevalence of 8.86%. For most patients, the episode was a recurrence. Two of the patients had lengthy treatments before the development of their manic symptoms, making it more difficult to attribute causation.

Preda and colleagues[14] evaluated all admissions to a general hospital psychiatric unit over a 14-month period and found that 8.1% (43/533) were admitted due to anti-

depressant-induced mania or psychosis. They estimated an incidence rate of 6.8%/year. Twenty-seven percent (12/43) were first-onset cases of mania. The SSRIs were the most common offenders, but all classes of antidepressants were represented.

By contrast, studies conducted for FDA approval of SSRI antidepressants show much lower rates. The label for paroxetine, for example, states, "During premarketing testing, hypomania or mania occurred in approximately 1.0% of unipolar patients treated with Paxil compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients."[15] Compared to treatment in routine clinical practice, studies used for FDA approval of antidepressants are usually relatively short in duration, exclude bipolar and suicidal patients, place limits on concomitant medications, and are more closely and regularly monitored, probably accounting in part for the lower rates for more severe adverse reactions.

The rate of occurrence of the broader activation or stimulation syndrome is not known. However, its occurrence is sufficiently frequent for the FDA to place great emphasis on it in its new label warnings for adults and children. The rates for the various symptoms of activation are almost always reported separately, but when added together they indicate that the syndrome is very common (Table).

TABLE

FREQUENT* ANTIDEPRESSANT ACTIVATION EFFECTS FROM THE 2001 PAROXETINE LABEL

Activation Effect	Rate (%)
Mania/hypomania	2.2% of bipolar patients
Mania/hypomania	1% of depressed patients
Insomnia	13%
Nervousness	5%
Anxiety	5%
Agitation	1%
Central nervous system stimulation	*
Emotional lability	*
Depression	*
Tremor	8%
Sweating	11%
Palpitation	3%

*Frequent means at a rate of ≥1%. Adverse drug reactions (ADRs) with percentages (%) are for depressed patients in placebo controlled clinical trials. ADRs without percentages are taken from the entire data pool of 7,678 patients administered paroxetine, including 6,145 depressed patients.

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Especially in regard to antidepressants with a known tendency to produce stimulation, including the SSRIs as well as venlafaxine and bupropion, physicians should remain alert for the development of medication-induced clinical worsening and stimulant-like reactions, especially early in treatment, during dose changes, or when other potentially stimulating agents are added to the medication regimen.

CONCLUSION

The FDA warned about the association of activation symptoms with dose changes. This confirms the need to avoid the hazards of abrupt withdrawal from the SSRIs. The physician should carefully monitor a gradual withdrawal, especially if patients have been exposed to these agents for months or years. If possible, a family member or friend should be involved because patients often do not attribute adverse drug reactions to the drug itself. Because activation reactions can pose a potential danger to the patient and to others, careful monitoring is advisable throughout treatment. Patients and families should be educated about activation, and the medication should be reduced or preferably stopped at the earliest sign of stimulation. ***PP***

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