

House Committee on Veterans' Affairs

Full Committee
February 24, 2010

Statement of Peter R. Breggin, M.D.

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I am Peter R. Breggin, MD, a psychiatrist in private practice in Washington, DC, for several decades and now in Ithaca, New York. In the early 1990s I became the first physician to speak and write extensively about the new antidepressants causing violence, suicide and other abnormal behavioral reactions. I became the scientific expert for more than one hundred combined cases against Eli Lilly concerning Prozac-induced violence and suicide, and wrote many related books and scientific articles. In 2004 the FDA finally upgraded the warnings for all antidepressant drugs. The FDA's language was virtually borrowed from one of my scientific publications (Breggin, 2003), which the agency had provided to each member of its review committee.

My conclusions in this testimony are based on dozens of citations listed in the scientific paper I have written specifically for this hearing, "Antidepressant-Induced Suicide and Violence: Risks for Military Personnel." My conclusions are further based on hundreds of scientific citations in my published papers and in chapters 6 and 7 of my 2008 medical book, *Brain-Disabling Treatments in Psychiatry, Second Edition* (New York: Springer Publishing Company).

My other recent book, *Medication Madness* (2008, New York: St. Martin's Press) presents more than 50 cases in which I have personally evaluated the medical and police records, and interviewed perpetrators and survivors. Based on voluminous scientific data and clinical experience, individuals with no prior tendencies toward suicide, violence or mania can be driven into these states by antidepressants.

In 2004 the FDA required the antidepressant manufacturers to review their previous clinical trials in regard to suicidality. The FDA concluded that the newer antidepressants **double** the rate of suicidal thoughts and behaviors in children, youth, and **young adults up to age 24**. The actual rates will be much more than doubled in routine clinical practice in the military and elsewhere. In routine practice the medications are administered for longer periods of time than a mere few weeks, monitoring is much more casual, drug cocktails are common, and suicidal and more disturbed patients are not excluded as they were in the clinical trials.

The FDA's new warnings provide a consensus of FDA-appointed experts. For convenience, I will cite the October 2008 FDA-approved label for Zoloft. The warnings are similar or identical to the other antidepressants. The Zoloft label begins at the top with the following Black Box bold warning:

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. ...

The black box is followed by a lengthy warning section ominously entitled **Clinical Worsening and Suicide Risk**. It states:

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.

For emphasis, the FDA repeats this array of dangerous symptoms throughout the label. Note the specific mention of irritability, hostility, aggressiveness, and impulsivity—a prescription for violence as well as suicide, especially in already stressed and heavily armed soldiers.

Federal regulations require that these warnings must be based on “reasonable evidence of a causal association with a drug.”

The FDA-approved label concludes with a Medication Guide that prescribers are advised to give and discuss with patients and their families. The guide lists the following risks associated with the drugs.

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Meanwhile, the efficacy of these drugs is in doubt for both children and adults. Under FDA regulations, pharmaceutical companies can cherry pick their studies to find only *two* that show minimal effectiveness. However, antidepressants do not prove effective compared to placebo when **all** controlled clinical trials conducted for the FDA are included in a meta-analysis.

As you may discover today, medical and psychiatric organizations that rely very heavily on financial support from the pharmaceutical industry have unconscionably resisted and even dismissed the FDA’s warnings, and all the science behind them.

In conclusion, there is overwhelming evidence that the newer antidepressants commonly prescribed in the military can cause or worsen suicidality, aggression, and other dangerous mental states. There is a strong probability that the documented increase in suicides in the military, as well as any increase in random violence among soldiers, is caused or exacerbated by the widespread prescription of antidepressant medication.

Little will be lost and much will be gained by curtailing the prescription of antidepressants in the military. The military instead should rely upon the newly developed psychological and educational programs described by Dr. Bart Billings at today’s hearing.

Antidepressant-Induced Suicide and Violence: Risks for Military Personnel

**By Peter R. Breggin, M.D. [[*\]](#)
Ithaca, New York**

I. Introduction

Evidence pertaining to violence and suicide induced by the newer antidepressants has been growing for years (Breggin and Breggin, 1994; Teicher et al., 2003). Recently public concern has been expressed about the increased prescription of psychiatric medications, especially antidepressants, to military personnel (Thompson, 2008). At the same time, the military has voiced concern about escalating rates of suicide

among active duty soldiers (Lorge, 2008). At a military conference on combat stress, this author pointed to an association between increasing rates of antidepressant prescription and increasing rates of suicide in the military (Breggin, 2009).

This paper focuses on evidence that antidepressants frequently cause suicide, violence and manic-like symptoms of over-stimulation—and therefore present a serious hazard when given to military personnel. Studies with children will be included, because they commonly involve youth up to age 17 or 18 and because medication risks for all age groups often show up first or most obviously among children.

II. Research Leads to FDA Label Changes for the Newer Antidepressants

A. FDA Label Changes

Because of concerns about reported cases of suicide in association with the newer antidepressants, the FDA required a re-evaluation of all controlled clinical trials conducted on children and youth during the FDA approval process. The selective serotonin reuptake inhibitor (SSRI) antidepressants were re-evaluated including fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro). In reports issued by the FDA (e.g., Food and Drug Administration, March 22, 2004d) four other potentially stimulating antidepressants were found to produce similar adverse behavioral and mental effects and were included in the group: venlafaxine (Effexor), mirtazapine (Remeron), bupropion (Wellbutrin or Zyban) and nefazodone (Serzone). The study included 4582 patients in 24 trials (Hammad et al., 2006). The meta-analysis found that the risk of suicidal ideation and behaviors was doubled for children and youth taking the antidepressants compared to placebo (4 percent versus 2 percent) (Food and Drug Administration, October 15, 2004a). The eventual label changes, however, were applied to all antidepressants, including older ones where no new evidence was available.

To illustrate the FDA-mandated label changes, the following excerpts are taken from the Zoloft (sertraline) label as of October 2008 (see attachments for complete label). Identical or nearly identical warnings and information can be found in all antidepressant labels, most of which appear in the *Physicians' Desk Reference*. A Black Box at the top of the label warns about the increased risk of suicidal behavior in children and youth, and also young adults ages 18-24, which includes many young soldiers.

The Zoloft label begins with the following Black Box Warning: [\[t\]](#)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. ...

The Black Box Warning provides additional information. Then the label continues with an elaborate **WARNINGS** section subtitled, **Clinical Worsening and Suicide Risk**, which contains the following statement:

There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders.

This section continues with a specific warning about the increased risk of medication-induced suicidality during “the initial few months of a course of drug therapy, or at times of doses changes, either increases or decreases.” It then describes an activation or stimulant-like array of adverse effects:

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.

Note the specific mention of “irritability, hostility, aggressiveness, impulsivity”—a virtual prescription for causing suicide and violence, especially in an already stressed individuals, including soldiers.

Further in the section on **Clinical Worsening and Suicide Risk**, this FDA-approved label recommends information that the prescriber should share with patients and caregivers. It repeats the array of dangerous stimulant or activation symptoms described above.

A section titled **Discontinuation of Treatment with Zoloft** describes similar dangers associated with stopping or withdrawing from Zoloft and the other newer antidepressants, including “dysphoric mood, irritability, agitation... anxiety, confusion... lethargy, emotional lability, insomnia, and hypomania.”

Under the heading **Information for Patients** the label addresses the importance of informing patients about all of these risks. In this section, the FDA-approved label once again warns about **Clinical Worsening and Suicide Risk** and again describes the activation syndrome, including “the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, 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.” It warns “families and caregivers of patients should be advised to look 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. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.”

The probability that these warnings will be given to military personnel is not high, and of course their families will often be unavailable to monitor them.

A Medication Guide appears at the end of the label. The label states, “The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents.” The Medication Guide is not restricted to any age group. Its application to all ages was confirmed in a communication from the FDA’s Senior Regulatory Project Manager, Division of Psychiatric Products to attorney Don Farber in 2008, which stated, “In 2007, FDA revised the MG [Medication Guide] to expand the age range to all patients. ... The revised MG was approved for all antidepressants in July and August 2007” (Grewal, 2008).

The Medication guide gives specific guidance about identifying danger signs associated with the use of antidepressants:

Call a healthcare provider right away if you or your family member has any of the following symptoms especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)

- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

To add to the risks, all of the above symptoms can occur when the dose is reduced or stopped. Withdrawal from antidepressants is very dangerous and must be done carefully and with supervision (Zoloft label; Breggin, 2008a&b).

Once again note the array of dangerous adverse reactions, including not only suicide but many emotional and behavior reactions that would be especially hazardous in a soldier, including, "feeling very agitated or restless," "new or worse irritability," "acting aggressive, being angry, or violent," and "acting on dangerous impulses "

B. Canadian Drug Regulatory Changes

On June 3, 2004, before the FDA issued its formal label changes, Health Canada (the Canadian drug regulatory agency) issued an Advisory for all of the newer antidepressants, including Zoloft, emphasizing the risk of both "harm to self" and "harm to others" in children and adults taking these drugs.

After consultations with Health Canada, Pfizer also upgraded its warnings for Antidepressant-Induced Suicide and Violence: Risks for Military Personnel

Zoloft on May 26, 2004. In a black boxed warning under the rubric "Adult and Pediatrics: Additional data," the company warns about the risk of "self-harm or harm to others." It too describes an activation or stimulant like array of drug-induced symptoms: "The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment."

III. Confirmation from the *Diagnostic and Statistical Manual of Mental Disorders*

The official American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (2000) is considered a consensus document drawing on current expertise in psychiatry. It is the most commonly used authority in the field and provides the official diagnostic system. In the section on mania and elsewhere, it makes clear that antidepressants can cause all the symptoms and behaviors associated with mania: "Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication..." (p. 361). Symptoms and behaviors associated with mania, including the medication-induced disorder, emphasize high-risk behaviors: "criminal" behavior, "antisocial" behavior, "irritability, particularly when the person's wishes are thwarted," "assaultive behavior," "physically assaultive" behavior, "physically threatening" behavior, "suicidal" behavior, and shifts from anger to depression (pp. 359-261). By causing mild to severe degrees of manic behavior, antidepressants can cause suicide, violence and a wide variety of antisocial behaviors.

The official diagnostic manual also makes clear that SSRI antidepressants can cause akathisia, including suicide, aggression, and worsening of psychosis or behavioral dyscontrol (American Psychiatric Association, 2000, p. 801).

IV. Overview of Scientific Studies

A. Antidepressant-Induced Suicidality in Children and Adults

In addition to the studies done under the auspices of the FDA (above), a large body of research confirms an increased risk of suicidality in children and adults (of all ages) when taking antidepressants. Aursnes et al. (2005) located unpublished data on adult controlled clinical trials not previously available for a total of 16 studies in which Paxil had been randomized against placebo. They found a statistically significant 7 suicide attempts among patients taking Paxil and 1 among patients receiving placebo. They concluded, "Our

findings support the results of recent meta-analyses. Patients and doctors should be warned that the increased suicidal activities observed in children and adolescents taking certain antidepressant drugs may also be present in adults."

Fergusson et al. (2005) searched the adult literature and found 702 randomized clinical trials (87,650 patients) comparing an SSRI to placebo or an active non-SSRI control medication. They found a statistically significant increased risk of suicide attempts on SSRIs compared to placebo.

Donovan, Kelleher, Lambourn, and Foster (1999) found a significantly increased rate of suicide among adult patients treated with SSRIs compared to those treated with tricyclic and other antidepressants. The large British study involved 222 suicides.

Donovan, Clayton, Beeharry, Jones, Kirk, Waters, et al. (2000) conducted a prospective study of 2776 consecutive cases of deliberate self-harm in individuals age seventeen and older who were seen at the emergency department of a British infirmary. The relative incidence of deliberate self-harm was significantly higher ($P < 0.001$) in patients who were prescribed the SSRIs fluoxetine, paroxetine, and sertraline compared to patients who were prescribed older more sedating antidepressants.

Jick, Dean and Jick (1995) conducted an epidemiological study of reports from general practices (primary care) in the United Kingdom involving 172,598 adult patients who had been given at least one prescription for antidepressants. Even after taking into account a past history of suicidal behavior and other variables, fluoxetine remained twice as likely to be associated with suicide as older more sedating antidepressants.

Frankenfield, Baker, Lange, Caplan and Smialek (1994) conducted a retrospective case review of all deaths in Maryland where either fluoxetine or tricyclic antidepressants were forensically detected. The study covered a three and one-half year period of time and found a statistically significant increase in *violent* suicides in association with fluoxetine (65 percent versus 23 percent).

Under guidance from the FDA, GlaxoSmithKline conducted "a new meta-analysis ... of suicidal behavior and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders..." (GlaxoSmithKline, 2006, p. 1). The company found a statistically significant increase in suicidal behavior in adults of *all ages* treated with Paxil for Major Depressive Disorder.

In a non-controlled study of suicide attempt cases admitted to a psychiatric unit in a general hospital, suicide attempt cases were more likely to have received antidepressants and benzodiazepines than non-suicide cases. The study noted the possibility that antidepressants and benzodiazepines "can induce, worsen or precipitate suicidal behavior in some patients..." (Raja et al., 2009, p. 37). It advised warning patients of the risk.

A study of 1,255 suicides in 2006 in Sweden (95 percent of all suicides in the country) examined the frequency of psychiatric medication usage up to 180 days before death (Ljung et al., 2009). The study reported that 32 percent of Scandinavian men and 52 percent of Scandinavian women filled a prescription for antidepressants in the 180 days prior to death by suicide.

A retrospective study examined the suicide rates among 887,859 VA patients treated for depression between April 1, 1999, and September 30, 2004. It focused on twelve-week periods after various events including hospitalization and antidepressant starts or dose changes. The authors found that "completed suicide rates were approximately twice the base rate following antidepressant starts in VA clinical settings" (Valenstein et al., 2009).

Juurlink et al. (2006) reviewed more than 1,000 cases of actual suicides in the *elderly* and found that during the first month of treatment the SSRI antidepressants were associated with nearly a five-fold higher risk compared to other antidepressants.

Fisher, Kent and Bryant (1995) conducted a phone survey of pharmacy patients taking various antidepressants and found a higher rate of suicidality on SSRIs.

The studies in this section confirm that the risk of antidepressant suicidality is not limited to children, youth, and young adults, but encompasses all ages.

B. Antidepressant-Induced Mania in Adults

A considerable body of research demonstrates that the newer antidepressants *frequently* cause mania. Preda, MacLean, Mazure, and Bowers (2001) carried out a retrospective study of 533 adult psychiatric hospital admissions over a fourteen-month period and found that 43 (8.1 percent) could be attributed to antidepressant-induced mania and/or psychosis. Morishita and Arita (2003) carried out a retrospective review of 79 patients treated for depression with paroxetine and found that 7 (8.6 percent) developed hypomania or mania.

Howland (1996) examined approximately 184 adult patients treated at a university clinic and hospital with SSRIs, including fluoxetine, paroxetine, and sertraline. He identified 11 cases (6 percent) of SSRI-induced mania, mostly severe.

Ebert et al. (1997) carried out a prospective study of 200 adult inpatients over a total of 8200 treatment days with the SSRI Luvox. Fourteen patients (17 percent) developed hypomania and some became potentially suicidal or dangerous.

Levy et al. (1998) carried out a blind retrospective chart assessment of 167 adult patients with anxiety disorders. They reported, "Five patients (2.99 percent) were identified as having an episode of antidepressant-associated mania within 3 months of initiation of treatment."

Martin et al. (2004) used a national database of more than 7 million privately insured individuals, aged 5-29 years, to find new diagnoses of bipolar illness made in association of antidepressant treatment. They found a statistically significant correlation between exposure to antidepressants and a subsequent diagnosis of bipolar disorder.

Individual who already have a tendency to become manic have *vastly* increased risk of mania when exposed to SSRI antidepressants (Henry et al., 2001; Ghaemi et al., 2000) with rates that exceed 20 percent.

The SSRI antidepressants pose a very serious, indeed an extreme, risk of causing mania in patients with and without a prior history of manic-like symptoms. This alone should contraindicate their use among active duty soldiers.

C. Antidepressant-Induced Aggression in Adults

Studies of antidepressant-induced mania often cite cases of violence. In addition, Healy et al. (2006) evaluated controlled clinical trial data produced by GlaxoSmithKline (2006a) concerning Paxil and found an increased rate of hostility for children and adults taking the medication. Healy (2000) conducted a randomized double-blind crossover study comparing the effects of sertraline (Zoloft) to a non-SSRI antidepressant (reboxetine) in a group of healthy volunteers. Many of the 20 individuals developed adverse mental and neurological effects while taking the sertraline and two became severely disturbed with tendencies toward suicidal and violent behavior.

The FDA conducted an unpublished epidemiological study comparing fluoxetine to trazodone in regard to spontaneous reports concerning hostility and intentional injury (Food and Drug Administration, 1991; available on www.breggin.com). Ever after the greater number of prescriptions for fluoxetine were factored in, fluoxetine had a higher frequency of reports for aggressive and violent behavior.

In a phone survey of pharmacy patients taking antidepressants, Fisher, Bryant and Kent (1993) compared fluoxetine with a more sedating antidepressant, trazodone. They concluded that fluoxetine caused "a higher incidence of psychologic/psychiatric adverse clinical events, including delusions and hallucinations, aggression, and suicidal ideation" (p. 235).

D. SSRI-Induced Apathy Syndrome in Adults

The mixture of apathy and disinhibited aggressiveness reported by Healy and others is found in a portion of patients who act uncharacteristically violent as a result of taking SSRIs (Breggin, 2008a&b). Hoehn-Saric, Lipsey and McLeod (1990) describe "Apathy and Indifference in Patients on Fluvoxamine and Fluoxetine," including apathy, indifference, loss of initiative and disinhibition with and without hypomania in five patients.

Antidepressant-induced apathy has become sufficiently common to be described in the American Psychiatric Press *Textbook of Psychiatry* (Marangell et al., 2003; also see Marangell et al., 1999). Patients who become apathetic lose their ability to care about others and may have an increased tendency toward both suicide and violent (Breggin, 2008b).

E. A Broad Range of Adverse Behavioral Effects in Children and Youth

Studies of children often include youth as old as age seventeen or eighteen. There are many studies confirming suicidality and aggression in children and youth (see earlier in this report and Breggin, 2008b). Also, children are often more sensitive to drugs and are more likely to display adverse effects that will also appear with less frequency in adults.

Researchers at Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital and Harvard Medical School systematically evaluated 82 charts of children and adolescents treated with SSRIs for depressive or OCD symptoms over a mean period of 26.9 months (Wilens et al., 2003). Psychiatric Adverse Events (PAEs) were found in 22 percent, "most commonly related to disturbances in mood." Remarkably, "Re-exposure to an SSRI resulted in another PAE in 44 percent (n=13) of the group." Of the 82 children, 21 percent developed *mood* disorders, including 15 percent who became *irritable*, 10 percent who became *anxious*, 9 percent who became *depressed*, and 6 percent who became *manic*. In addition, 4 percent of the children became *aggressive*. *Sleep* disorders afflicted 35 percent of the children, including 23 percent *drowsy* and 17 percent *insomnia*. Finally, 10 percent became *psychotic*!

Go et al. (1998) reviewed the cases of 40 youths, ages 12-18, treated with antidepressants for OCD. Thirty percent (6 of 20) developed hypomanic or manic symptoms. Jain, Birmaher, Garcia, Al-Shabbout and Ryan (1992) made a retrospective examination of the medical charts of children and young men age 9-18, who had taken fluoxetine at university clinic. The researchers found that 23 percent of fluoxetine-treated young people developed mania or manic-like symptoms. Another 19 percent developed drug-induced hostility and aggression, including a grinding anger with short temper and increasing oppositional behavior.

Constantino, Liberman and Kincaid (1997) prospectively studied the course of aggressive behavior in nineteen SSRI-treated psychiatrically hospitalized adolescents, age 13-17. The group was not pre-selected for potential aggressiveness. They found symptoms of physical aggression toward self or others in 12 of 19 patients on SSRIs.

Another study of children and youth age 8-16 in a university setting found that 50 percent developed two or more abnormal behavioral reactions to fluoxetine, including aggression, loss of impulse control, agitation, and manic-like symptoms (Riddle, King, Hardin, et al, 1990/1991). The effects lasted until the fluoxetine was stopped.

A second research study from the same university setting described a number of youngsters (6 of 42 or 14 percent in their cohort) age 10-17 who became aggressive and even violent while taking fluoxetine (King, Riddle, Chappell, et al., 1991).

A controlled clinical trial found that fluoxetine caused a 6 percent rate of mania in depressed children and youngsters age 7-17 (Emslie et al., 1997), causing the youngsters to be removed from the study.

As already mentioned, Martin et al. (2004) studied a national database for more than 7 million privately insured individuals, aged 5-29 years, and found that exposure to antidepressants increases the probability of a subsequent diagnosis of bipolar disorder.

In combination with the FDA's suicide warnings in regard to children, youth, and young adults, the studies in this section should lead to the discontinuation of antidepressants in the treatment of children and youth.

V. Determining Causation for Drug Research

A. Bradford Hill Criteria for Causation

The nine Bradford Hill criteria for causation (Reekum, et al., 2001; Bailey et al., 1994) were easily met by the FDA studies on antidepressant-induced pediatric suicidality as well by the great majority of studies reviewed in this report concerning antidepressant-induced suicidality, mania, aggression, and other behavioral disturbances both in children and in adults. The one exception was the Bradford Hill criterion called "Specificity," which is described by the authors as outmoded. Although not all of the criteria must be met to confirm causality, each of the studies do fulfill all or most of criteria, including Strength of the Association, Consistency of Evidence, Temporal Sequence, Biological Gradient, Biologic Rationale, Coherence, Experimental Evidence, and Analogous Evidence.

Although it is a rare occurrence in psychiatry, the research on antidepressant-induced suicidality and mania in children and adults even meet the most stringent and convincing Bradford Hill criterion—Experimental Evidence (Reekum, et al., 2001):

Experimental evidence is the most compelling evidence of causation. If it can be shown that experimentally (ideally randomly) inducing the causative agent consistently produces the outcome, at greater rates than in a nonexposed control sample, this is clear and compelling evidence of causation. However, it is obvious that such evidence will be rare in neuropsychiatry... P. 8

The capacity of controlled clinical trials to establish causality was confirmed in a discussion between FDA officials Russell Katz, MD, Director of Neurological Products, and Ralph Temple, MD, Director of Medical Policy, the Center for Drug Evaluation and Research. The verbal exchange took place during an FDA Advisory Committee Meeting (Joint Meeting of the Peripheral Nervous and Central Nervous System Drugs Advisory Committee... 2006, pp. 274 and 275). Katz and Temple agreed that when "controlled clinical trials" demonstrate a statistically significant difference from placebo, then "that is operationally defined as causality."

B. Causation in Regard to the FDA Suicide Studies of Children and Youth

The FDA-mandated review of all placebo-controlled antidepressant clinical trials for children, youth and young adults strongly established the causal relationship between the newer antidepressants and suicidality. Thomas Laughren, at the time the Director, Division of Psychiatric Products of the FDA, wrote, "The pediatric data presented at the September 2004 PDAC meeting represented the first systematic demonstration of a *causal* link" (Laughren, 2006, emphasis added). Cynthia Pfeffer (2007), a physician and consultant to the FDA meetings, stated in regard to the pediatric trials, "The committee concluded that a causal link exists between antidepressant treatment and pediatric suicidality..." (p. 844). Thomas Newman (2004), a physician and epidemiologist on the FDA Advisory Committee further observed, "The fact that an association emerged from the meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials [pharmaceutical companies] were not looking for, and presumably did not wish to find, was quite convincing" (p. 1598).

The FDA Advisory Committee voted 25-1 with 1 abstention for "Yes" in response to the question, "Do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients?" It then voted 27-0 that "we are unable to conclude that any single antidepressant agent is free of risk at this time" (Food and Drug Administration, 2004c, "Questions to the Committee," unnumbered).

Five members of the Advisory Committee wrote a review of the FDA's deliberations concerning antidepressant-induced suicidality in children and youth (up to age 18), and made clear that causation had been established (Leslie et al., 2005). They stated, "the causal link demonstrated in the FDA analyses therefore focused entirely on suicidal ideation and behavior" (p. 200) and that "there was an increased risk

for suicidality causally related to the use of the SSRIs and related antidepressants" (p. 200).

The FDA originally required the pharmaceutical companies to state in their antidepressant labels that "A causal role for antidepressants in inducing suicidality has been established in pediatric patients" (Food and Drug Administration, October 15, 2004b). Later this wording was modified to an "increased the risk," which is substantially the same. The FDA's definitive publication on its findings speaks directly of "the absolute increase in the risk of the event of interest due to treatment" (Hammad et al., 2006). The FDA report concluded, "when considering 100 treated patients, we might expect 1 to 3 patients to have an increase in suicidality beyond the risk that occurs with depression itself owing to short-term treatment with an antidepressant" (p. 336).

Under clinical conditions in the real world rather than in controlled clinical trials, the rates of suicidality would be much higher than those in the clinical trials. Controlled clinical trials educate and inform the patients in detail, involve weekly monitoring, last no more than several weeks, avoid drug combinations, and exclude suicidal patients. In addition, they provide great hope and inspiration to the subjects and their families who seek to find a "new cure" for their emotional problems by participating in the experimental clinical trials (Breggin, 2008b). Because of these factors it is very rare for a patient to actually commit suicide during a trial, and none occurred in FDA's pediatric trials.

C. FDA Warnings for Children, Youth and All Adults

We have seen that the FDA-approved labels for Zoloft and all other antidepressants contain elaborate warnings about medication-induced suicidality in children, youth and young adults, as well as warnings for a wide array of other symptoms including impulsivity, hostility, aggressiveness, and mania. The federal regulations that govern the warnings sections in drug labels dictate that the inclusion of these adverse reactions must be based on "reasonable evidence of a causal association with a drug." According to the Code of Federal Regulations (2008):

In accordance with Sec. Sec. 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.
P. 29

In a Talk Paper, the FDA confirmed that the array of stimulant-like or activation symptoms associated with the antidepressants was in fact caused by the drugs when it referred to "certain behaviors *known* to be associated with these drugs, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania..." (FDA, 2004d, p. 1, emphasis added).

This array of activation or stimulant-like symptoms is described in the antidepressant labels as occurring in children and adults. Consistent with this, the Talk Paper stated, "The agency is advising clinicians, patients, families and caregivers of *adults* and children that they should closely monitor all patients being placed on therapy with these drugs for worsening depression and suicidal thinking, which can occur during the early period of treatment" (FDA, 2004d, p. 1, emphasis added).

VI. Case Examples

A. Causation Established by Clinical Case Reports

The pharmaceutical industry has attempted to discredit case reports as evidence for causation. However, case reports have led to most FDA changes in labels and to most withdrawals of psychiatric drugs from the market, and are a mainstay in the FDA for evaluating adverse drug reactions (Food and Drug Administration, 1993 & 1996; Government Accounting Office, 1990; Breggin, 2008b, pp. 263-269). The FDA itself described principles for determining causation from clinical reports (now called adverse event reports) in a table titled "Useful Factors for Assessing *Causal* Relationship Between Drug and Reported Adverse Event" (Food and Drug Administration, 1996, p. 6, emphasis added). Drawing on an international consensus meeting on the subject (Standardization of Definitions and Criteria of Causality Assessment of Adverse Drug Reactions, 1990), the FDA listed six potential criteria: chronology or temporal relationship,

course of event when agent stopped (dechallenge), known etiological roles of agents in regard to the event, response to readministration of the agent (rechallenge), laboratory test results, and “previously known toxicity of agent.”

Because clinical trial, epidemiological and other research evidence is so strong in regard the antidepressant-induced mental and behavioral abnormalities, the following clinical cases are included mainly for illustrative purposes.

B. Clinical Cases

In my clinical and forensic practice I have evaluated more than fifty cases of violence, suicide, mania and crime induced by psychiatric medications, especially the newer antidepressants (Breggin, 2008a). In the cases that I reviewed, the suicidal, violent or criminal behaviors were unprecedented and seemed in retrospect to be very alien and inexplicable to the individuals. Recidivism was zero when the medications were stopped. In evaluating the cases, I interviewed surviving victims and their families and acquaintances. In all but one of the cases I had complete access to medical, educational, occupational and police records. In all cases I interviewed the individuals if they survived, as well as witnesses and family members. In many cases my expert reports lead to acquittal on the basis of involuntary intoxication, reduced charges, shortened sentences, or release from incarceration. Most of the cases were evaluated for legal purposes and some were clinical consultations or treatment cases.

As the patterns emerged from re-examining these cases, I was struck by the fact that victims of drug-induced abnormal mental states and behavior almost never had an inkling that they were acting irrationally or that they were under the influence of their psychiatric drugs. This led me to formulate the concept of medication spellbinding (intoxication anosognosia)—the concept that psychoactive substances reduce the individual’s capacity to appreciate mental and behavioral adverse reactions (Breggin, 2006, 2008a&b).

Case A: A gentle thirty-seven year old man with previously mild depressive symptoms and no history of violence became psychotic shortly after starting the SSRI antidepressant sertraline (Zoloft) and believed that his wife had been taken over by a dangerous alien from another world. In order to destroy the alien inside her, he undid her safety belt and drove their car into a barrier, nearly killing her. In a legal case in which I played no role, he was found Not Guilty by Reason of Insanity. Only after he began to recover over the subsequent weeks of psychiatric incarceration did he begin to suspect that medications might have caused his psychosis. He was released after several months of commitment to a mental hospital whereupon he was referred to me to gradually remove him from a cocktail of medications. He has done very well after more than a decade of drug-free follow-up.

Case B: Without using a disguise, a twenty-year old college man with no history of crime committed a series of eight knife-point robberies of his local gas stations, including those he and his family frequented, and was easily identified and caught. He had been recently started on the SSRI antidepressant paroxetine (Paxil) which was continued during his trial and sentencing. He was allowed to return home briefly before serving a lengthy incarceration and immediately robbed another local gas station using an identical knife and the same automobile, and was easily apprehended. My report on the effects of Paxil on his behavior convinced the court to give him a considerably reduced sentence.

The above cases had manic features. In other cases, compulsive suicidal or violent behaviors developed without associated manic-like features.

Case C: A sixteen-year-old girl was begun on fluoxetine (Prozac) to relieve the stress associated with an undiagnosed gastrointestinal disorder. Although there were no serious conflicts in the family, shortly after starting on the fluoxetine, she began to feel intensely compelled to stab her mother in the back. As the urge peaked, she confessed her intentions to her mother, and completely recovered when removed from the antidepressant.

Case D: A thirty-eight year old highly responsible man with minimal symptoms of depression and no history of crime or violence was prescribed sertraline (Paxil). Within weeks the medication caused him to suffer from akathisia (extreme restlessness and agitation) and obsessive suicidality. He drove his car into a

policeman in order to knock him down to obtain his gun to shoot himself. The officer was seriously injured but with the help of a bystander he managed to subdue his assailant. After my expert report in the case, the police officer agreed that drugs must have caused the assault, and a plea agreement was reached that led to only a brief incarceration. On follow up he has done well for several years.

Familiarity with medication effects does not necessarily protect the individual from abnormal emotional and behavior reactions. In several of my cases (Breggin, 2008a), the victims of drug-induced abnormal behaviors were physicians.

Case E: A sophisticated psychiatrist with no history of violence gradually became manic while taking the SSRI antidepressant fluvoxamine (Luvox). He violently assaulted a female colleague with a tack hammer and then made a bizarre suicide attempt. He was convicted of assault and continued on the antidepressant in prison. He remained in a medication-induced mildly manic-like condition in prison and did not realize that the drug had caused his violent behavior until he was removed from it several months later. While still incarcerated, he asked me for a consultation to clarify what had occurred.

VII. Antidepressant-Induced Reactions that Result in Suicide and Violence

The various antidepressant-induced clinical syndromes and reactions associated with suicide and violence have been reviewed elsewhere (e.g., Teicher et al., 1990, 1993; Breggin, 1993 and 2008a&b). Almost all are now described in the FDA-mandated label changes under **Clinical Worsening and Suicide Risk**, including the activation or stimulation spectrum of adverse drug effects: "the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, 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."

All of the above adverse reactions are associated with suicide and violence. The antidepressant labels confirm that these can occur when the drug is given for " both psychiatric and nonpsychiatric" purposes. In a study of patients treated with fluoxetine and paroxetine, and suffering from nothing more than learning disabilities, 31 percent suffered from stimulant symptoms including elevated mood, hyperactivity, overtalkativeness, agitation, and aggression (Biswas et al., 2001).

Individually, some of the causal syndromes or adverse reactions include: (1) anxiety and agitation with or without hyperactivity (akathisia); (2) worsening depression; (3) compulsive suicidality, (4) irritability, hostility, and aggressiveness, (5) apathy and indifference, (6) behavioral dyscontrol or impulsivity, and (7) mania and psychosis.

VIII. Lack of Efficacy

It is relatively easy to prove that antidepressants frequently cause serious and even life-threatening harm, while it remains difficult to prove that they are helpful. In order to obtain FDA-approval, pharmaceutical companies cherry pick their studies in order to find two that show some effectiveness. However, when all adult controlled clinical trials, including the unsuccessful ones, are pooled in a meta-analysis, antidepressants do not prove effective (Kirsch et al., 2008; Moncrief and Kirsch, 2005). Meanwhile, studies of children and youth almost uniformly fail to show effectiveness (Whittington et al., 2004, ages 5-18; Jureidini et al., 2004, Tonkin and Jureidini, 2005; studies reviewed in Breggin, 2008b).

IX. Conclusion

There is overwhelming evidence that the SSRIs and other stimulating antidepressants cause suicidality and aggression in children and adults of all ages. The evidence suggests that young adults aged 18-24 (the age of many soldiers) are especially at risk for antidepressant-induced suicidality. There is a strong probability that the increasing suicide rates among active duty soldiers are in part caused or exacerbated by the widespread prescription of antidepressant medication. In addition, antidepressants frequently cause manic-like reactions, including loss of impulse control and violence, posing potentially grave risks among military personnel. Little will be lost and much will be gained by stopping the prescription of antidepressants to military personnel. The military should rely upon the psychological and educational programs that are

currently under development for preventing suicide and ameliorating other psychiatric disorders among service members. Antidepressants should be avoided in the treatment of military personnel.

X. Bibliography

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[†] Bold emphases also appear in the label.