International Journal of Risk & Safety in Medicine 16 (2004) 247–259
IOS Press

Recent U.S., Canadian and British regulatory agency actions concerning antidepressant-induced harm to self and others: A review and analysis [1]

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1. Introduction

Drug regulatory agencies in the United States (FDA), Canada (Health Canada) and Great Britain (MHRA) have significantly upgraded their warnings concerning antidepressant-induced suicidality in children. Furthermore, the U.S. and Canada have confirmed an antidepressant-induced stimulant or activation cluster of adverse events in children and adults that includes hostility and aggression. Although most attention has been given to warnings about drug-induced suicidality, more emphasis needs to be placed upon U.S. and Canadian warnings about the potential production of stimulation and mania with hostility and aggression. This report examines these recent regulatory events and related research. It also updates the author's most recent review of antidepressant-induced behavioral and mental abnormalities [6].

The SSRIs (selective serotonin reuptake inhibitors) have been the major focus of attention by the regulatory agencies. With some exceptions in regard to the severity or frequency of adverse reactions, the SSRIs can be treated as one group in regard to their profile of adverse drug reactions[2]. The SSRIs include fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escilalopram (Lexapro). In recent reports issued by the FDA [14] 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), Wellbutrin or Zyban (bupropion) and nefazodone (Serzone).

[1]The present paper appears simultaneously in *Ethical Human Psychology and Psychiatry*, Journal of the International Center for the Study of Psychiatry and Psychology and is published with permission of Springer Publishing Company, New York, NY, USA.

[2]Marangell, Yudofsky and Silver [30] observed, "All SSRIs have a similar spectrum of efficacy and a similar side-effect profile" (p. 1035). Exceptions include the greater withdrawal problems associated with shorter acting SSRIs (e.g., Paxil) and the greater severity and/or frequency of psychiatric adverse reactions associated with some (e.g., Paxil).

2. Recent research findings

2.1. Healy reevaluation of SSRI clinical trials for Paxil-induced suicidality and violence

2.1.1. Suicide and suicidal acts

Healy and Whitaker [21] reviewed all available meta-analyses, epidemiological studies and randomized controlled trials (RCTs) to determine if SSRI antidepressants increase the rate of suicide and suicidal acts. In one analysis, they pooled the data previously obtained from the FDA database for antidepressants [25–27]. For all SSRIs, suicides and suicide attempts occurred in 1.53% of patients and for placebo they occurred in 0.47% of patients. The odds ratio for a completed suicide while taking an SSRI antidepressant (including venlafaxine) compared to placebo was 2.46. The odds ratio for suicidal acts was 2.22 compared to placebo. In comparing all of the new antidepressants to placebo, the odds ratio for a suicide was 4.40 ($p = 0.0125$) and the odds ratio for suicidal acts was 2.39 ($p \leqslant 0.0001$). All of the newer antidepressants had higher percentage of suicide and suicidality than placebo: sertraline (0.44%/0.25%), paroxetine (1.52%/0.54%), nefazodone (0.60%/0.11%), mirtazapine (1.53%/0.61%), citalopram (2.38%/1.59%), fluoxetine (0.91%/0%) and venlafaxine (1.40%/0.41%). The relative risk of suicidal acts was statistically significant for sertraline, paroxetine and fluoxetine compared to placebo. For bupropion there were three suicides in the treatment group and none in the placebo group, and no data on suicide attempts.

Healy and Whitaker [21] also re-evaluated epidemiological studies from the United Kingdom. They found increased rates of suicide and suicidal behavior on SSRI antidepressants.

In a letter to the FDA Healy [20] reviewed all available Paxil (British trade name Seroxat) controlled clinical trials for SSRIs for children and teenagers. In Protocol 329 (1993-late 95/early 1996) Paxil was ineffective in children. According to Healy, "The results in terms of hazards were also conclusive; Seroxat/Paxil had a statistically significant excess of suicidal acts compared to comparators" (p. 5). There were five suicidal acts among 93 drug-treated children, none among 89 children on placebo, and one among 184 children on placebo or imipramine. "Furthermore roughly 10% of the children had psychiatric side effects on Seroxat/Paxil, which is particularly significant against a background of failure to demonstrate that the drug worked" (p. 5).

Healy pointed out, "In the published version of 329 [24], suicidality disappears under a carpet of emotional lability" (p. 5). After Protocol 329 was disclosed on British television (Panorama), the MHRA obtained the suicide data hidden under the term "emotional lability", leading the agency to issue its first warning about Paxil.

Healy also reported that other protocols that may have been even more negative than Protocol 329 (e.g., Protocols 377, 511, and 716) were never made available to regulatory agencies or published. He found a systematic attempt by the manufacturer GlaxoSmithKline to hide the risk of suicide by recoding suicidal behavior as emotional lability.

Healy pooled all available data from controlled clinical trials for the treatment of depression in children involving several SSRIs (Paxil, Zoloft, Celexa, and Prozac). He reviewed 931 depressed children treated with SSRIs and 811 treated with placebo. There were 52 suicidal *acts* on SSRIs compared to 18 on placebo for a comparative rate of 5.6% versus 2.2%. The odds ratio was 2.51 ($p = 0.000899$).

Healy also pooled data from clinical trials for the treatment of anxiety in children. There were 10 suicidal acts among 638 anxious patients treated with SSRIs and one among 562 taking placebo. The comparative rates were 1.6% versus 0.18% for an odds ratio of 11.31 ($p = 0.0156$).

When the depressed and anxious pediatric patients were combined, there was a 4% rate of suicidal acts in the treated group and 1.4% in the placebo group. The relative risk for suicidal acts among the children was 2.9 times greater for SSRIs.

Healy found "While the rate of suicidal acts is higher in pediatric trials of depression, the relationship between active treatment and placebo is the same in both adult and pediatric groups" (p. 9). In addition, the rate in children increased from the 6–12 age group to the teenage years, indicating that the problem worsened with age.

2.1.2. Aggressive acts

In Protocol 329 and other Paxil pediatric studies Healy [20] found that "aggressive events appear under the heading of hostility, a term that covers homicidal acts, homicidal ideation and aggressive events" (pp. 5–6). Healy analyzed data on acts of hostility from four different protocols on GlaxoSmithKline's website, plus one additional protocol. He counted 31 reported hostile episodes among 524 Paxil-treated patients and only 2 among 526 placebo patients. The odds ratio was 15.54 ($p = 0.000001$). Healy states: "These results are in line with the analyses of data conducted by Andrew Mosholder of the FDA and by the MHRA, but excludes a number of drugs these authors included. This analysis represents a much purer set of SSRI drugs, and more data on SSRI drugs than has been available to other reviews" (p. 10).

Healy emphasized that SSRI-induced agitation tends to be dose dependent in healthy volunteers and patients (making suicidal and violent acts potentially dose dependent). He found that a large proportion of these adverse events take place early in treatment or during dose changes, including reductions or withdrawal.

2.2. Jureidini et al. (2004) review the risk/benefit ratio

Jureidini et al. [23] reviewed the literature and found six placebo-controlled clinical trials for children involving the newer antidepressants. Their analysis concluded that a "major benefit" from these drugs was unlikely and that the adverse effects reported in the clinical trials outweighed any possible "small benefit". They came out against recommending antidepressants as a "treatment option, let alone as first line treatment" (p. 882). In summary, "Antidepressant drugs cannot confidently be recommended as a treatment option for childhood depression" (p. 879). They found that "Adverse effects have been downplayed" and observed that "A more critical approach to ensuring the validity of published data is needed" (p. 879). Among the adverse effects, they cited the activation syndrome.

2.3. Whittington et al. (2004) metanalysis of the risk/benefit ratio

Whittington et al. [37] conducted a metanalysis of data from placebo-controlled clinical trials in children that were published in peer-reviewed journals or included in a review of unpublished studies on the website of the Committee on Safety of Medicines (CSM, Great Britain). They found that the data supported a "favourable risk–benefit" ratio for Prozac on the basis of two published clinical trials, as well as unpublished data. They found equivocal, weak, or unfavourable risk–benefit profiles based on studies of paroxetine, sertraline, citalopram and venlafaxine. They concluded, "Greater openness and transparency with respect to all intervention studies is needed" (p. 1341).

Whittington and his colleagues should have included Prozac among the drugs with unfavorable risk–benefit ratios; but they may have missed an observation buried in the discussion of dropouts in a paper by Emslie et al. from 1997 indicating that 6% of the children discontinued because of manic symptoms [13]. This is an extraordinarily high frequency for a very dangerous adverse reaction.

In addition, in a prepublication paper delivered at a psychiatric conference prior to the publication of his study in 1997, Emslie reported in 1995 that the clinical trial found not only a 6% rate of mania but an increased rate of aggression in children taking Prozac [11]. However, he failed to make any mention of the increased aggression in the published version [13]. In response to Emslie's prepublication remarks, I wrote a letter to Clinical Psychiatry News challenging Emslie's conclusion that Prozac was safe for children despite drug-induced aggression and mania [5]. At the conclusion of my letter, the editors commented that Emslie "declined to respond".

Jureidini et al. [23] point out that funding for the 1997 Emslie et al. publication was "attributed to National Institute of Mental Health, but that FDA data show the study was sponsored by Eli Lilly" and that funding for an other publication on the subject by Emslie et al. [12] came directly from the drug company with "all authors employed by or otherwise contracted to Eli Lilly" (Table, p. 880). Eli Lilly has a history of hiding suicidality data in its Prozac trials under false headings such as no drug effect [3,20].

2.4. Moore's (2004) analysis of FDA spontaneous reporting system data

Moore [33] analyzed all spontaneous reports to the FDA for the six most commonly prescribed antidepressant drugs: sertraline, paroxetine, fluoxetine, citalopram, bupropion, and venlafaxine. From November 1997 through December 2002 the FDA received 44,026 reports. Children accounted for 5.2% of all reports. Key findings of the study included the following (p. 1):

- Among all ages, the six target drugs were suspected of triggering 3,309 episodes of suicide, attempted suicide, or hostile, violent or other abnormal behaviors. A total of 353 cases were in children under 18 years of age.
- Suicidal/aggressive behaviors were reported in children at more than twice the expected rate given the drugs' medical use in this group.
- Like suicidal/aggressive behaviors, mania/euphoria was also reported more than twice as frequently as expected in children.
- Taken together, suicidal/aggressive behaviors and mania/euphoria describe potentially dangerous changes in mood or personality suspected of being associated with the six target drugs. In children, such reports accounted for 24% of all reported adverse events.

Taken in the context of other confirmatory findings, Moore believes that the evidence provides a strong warning signal concerning the potential of the newer antidepressants to cause suicidal, aggressive, and manic behaviors in children.

3. FDA-sponsored research presented at the September 13–14, 2004 FDA hearings

3.1. The Columbia project

At the follow-up FDA hearing on September 13, 2004, Hammad [18] reported in 2004 on the FDA-sponsored Columbia project that analyzed 25 trials with pediatric patients from nine drug development programs. The project also performed a reclassification study of drug company adverse reaction reports for Prozac. The Columbia project found that the antidepressants produced a statistically significant 2–3% increase in the risk of suicidality in children, including suicidal ideation and actions. There were no completed suicides in the group.

3.2. Mosholder studies of SSRI-induced suicidality

Mosholder of the FDA Office of Drug Safety (ODS) conducted an in-house study that indicated an increased rate of suicidality for SSRIs in controlled clinical trials [34]. The FDA did not allow Mosholder to publish his results or to present them at the initial FDA hearing on February 12, 2004. At the follow-up FDA hearing on September 13, 2004 Mosholder presented his findings, bolstered with additional data from the Columbia study of suicidality in pediatric trials and an officially approved FDA analysis by the Division of Neuropharmacologic Drug Products (DNDP) [35]. Mosholder and the DNDP evaluated all available clinical trials for sertraline, paroxetine, fluoxetine, citalopram, and venlafaxine. Mosholder concluded that his original ODS study and the more recent DNDP analysis both indicated an association of suicidality with antidepressant drug treatment in short-term, placebo-controlled trials in children and adolescents under age eighteen (pediatric patients).

Based on the Columbia, ODS and DNDP studies, Mosholder calculated the risk as equivalent to one event of suicidality for every twelve years of patient treatment.

3.3. The actual rates of suicidality are higher

The estimated rates for suicidality in the Columbia, Mosholder and DNDP studies are far below the actual rates. The available data was not based on the original clinical reports from the principal investigators in the field. Instead, the researchers relied on summaries of these events written by drug company officials. However, drug company officials have laundered suicidality data for Prozac [12] and for Paxil [20,28] by coding them under misleading terms such as no drug effect (Prozac) or emotional lability (Paxil). Furthermore, the dropout rates in Prozac studies have been very high, and follow up studies on the dropouts non-existent, so that it is impossible to know how many suicidal acts took place a day or more afterward in patients who dropped out in a worsened condition. On page 9 of the report by Healy in 2004 [20] one can read that Eli Lilly (Prozac) and GlaxoSmithKline (Paxil) submitted suicide data for placebo groups that originated before or after rather than during the clinical trials. Furthermore, Healy noted that the FDA-sponsored analyses ignored the impact of dose reduction and withdrawal although GlaxoSmithKline in its letter to healthcare professions in Great Britain states that dose lowering may lead to suicidality.

The FDA has not done any follow-up studies of adult patients and has thus far refused offers from this author [8] and from the British Medical Journal [29] to produce drug-company generated data indicating increased suicide rates among adults exposed to SSRIs.

3.4. Laughren's observations

Thomas Laughren [28], Team Leader of the FDA's Psychiatric Drug Products Group, Division of Neuropharmacologic Drug Products, noted at the September 2004 FDA hearings that suicidality was especially a problem "at the beginning of therapy, or at times of dose changes". He also emphasized the risk "in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms". He further connected suicidality to the development of the stimulant or activation syndrome: "Observe for emergence of other symptoms as well, including: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania" (p. 2).

Laughren confirmed the failure to find efficacy demonstrated for any of the drugs in the pediatric trials. Only three of fifteen trials reviewed were positive for efficacy in children suffering from major depressive disorder.

4. The FDA takes action

4.1. The FDA public health advisory describes activation (stimulant) syndrome

On March 22, 2004 the FDA published a Talk Paper entitled, "FDA Issues Public Health Advisory on Cautions for the Use of Antidepressants in Adults and Children" [14]. Note that the advisory focused on *adults* as well as children. The FDA 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 anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania".

The FDA describes these adverse reactions as "known" – that is, scientifically demonstrated or established. The list confirms the existence of the antidepressant-induced stimulant effect or activation syndrome[3] in adults and children with its potential to cause hostility and related behaviors.

4.2. The implications of irritability, akathisia and mania

Three specific terms that appear in several FDA publications are closely related to violence. First, the term "irritability" when used in psychiatry specifically includes heightened aggression. The American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders, IV-TR* (*DSM-III-TR*)[4] [1] , for example, defines irritability as "persistent anger, a tendency to respond to events with angry outbursts or blaming others, or an exaggerated sense of frustration over minor matters" (p. 349).

Second, "akathisia" is also associated with violence. Akathisia is a drug-induced state of inner irritability and agitation that usually (but not always) manifests itself in hyperactivity. The *DSM-III-TR* states that SSRI antidepressants can cause akathisia and that akathisia can result in severe behavioral abnormalities, including suicide and aggression: "Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts. It also described, "worsening of psychotic symptoms or behavior dyscontrol" (American Psychiatric Association [1, p. 801]).

Third, drug-induced mania can cause violence and suicide. The *DSM-III-TR* contains many references to antidepressant-induced mood disorders including mania and depression (e.g., American Psychiatric Association, 2000, pp. 361 and 406; footnotes on charts, pp. 362, 365 and 368). For example, the *DSM-IV-TR* section on Manic Episode reaffirms, "Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication . . ." (p. 361). The same section observes that manic episodes can produce "assaultive behavior" (p. 358) and "The person may be hostile and physical threatening to others. Some individuals, especially those with psychotic features, may become physically assaultive or suicidal" (p. 359). Also, "Mood may shift rapidly to anger or depression" (p. 359).

[3]Chesney, in 2004 [10], speaking on the Pediatric Drug Committee at the FDA hearings, confirmed that the advisory committee considered aggression and hostility to be aspects of the activation syndrome.

[4]The *DSM-III-TR* represents a scientific consensus of experts in the field. The introduction states, "The utility and credibility of DSM-IV require that it focus on its clinical, research, and educational purposes and be supported by an extensive empirical foundation" (p. xxiii). Furthermore, it states, "It must be noted that the DSM-IV reflects a consensus about the classification and diagnosis of mental disorders derived at the time of its initial publication" (p. xxiii). The *DSM-IV-TR* endorses its application to the legal arena: "By providing a compendium based on a review of the pertinent clinical and research literature, DSM-IV may facilitate the legal decision-makers' understanding of the relevant characteristics of mental disorders" (p. xxiii).

4.3. The FDA further confirms SSRI-induced abnormal behavior, including violence and aggression

Following its March 22, 2004 Public Health Advisory, the FDA continued to emphasize its conclusions that SSRIs can cause suicidality in children and a variety of stimulant or activation symptoms in adults and children that are implicated in both suicide and violence.

On October 15, 2004 (updated October 28, 2004) the FDA made official its "labeling change request" for antidepressants requiring drug companies to update their labels with specific language [16]. In its highest level of warning, a black box, the FDA unequivocally endorsed causality for antidepressant-induced suicidality: "Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders" (p. 1).

The FDA labeling request also includes the following: "All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug treatment, or at times of dose changes, either increases or decreases" (p. 2).

The label update suggested changing the therapeutic regimen, or stopping the medication, in medicated patients with worsening depression or suicidality "especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms" (p. 3).

The new antidepressant labels will also be required to contain the following warning statement about activation or stimulation, including hostility and aggression: "The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggression), 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 non-psychiatric" (p. 3).

The reference to "non-psychiatric" indications confirmed that the activation syndrome, including hostility and aggression, can occur in patients who have not been given psychiatric diagnoses. This contradicted the myth that these reactions are confined to mentally disordered individuals and specifically individuals who are being treated for depression.

In its letter requiring a label change, the FDA also summarized the results of its analyses of controlled clinical trials presented at the September 2004 hearing [15]: "Pooled analyses of short-term placebo controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD and other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk or 2%. There was considerable variation in risk among drugs, but a tendency toward an crease for almost all drugs studied".

The FDA repeated and summarized these themes in the label section on information for patients and their families: "Patients and their families should be encouraged to be alert for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, 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 physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms" (p. 5).

On November 3, 2004, the FDA published its "FDA Proposed Medication Guide: About Using Antidepressants in Children and Adults" [17]. In a heading entitled "What to Watch out for in Children

or Teens Taking Antidepressants", it listed twelve items with bullets. Four are especially relevant to the production of violence:

- Feeling very agitated or restless;
- New or worse irritability;
- Acting aggressive, being angry, or violent;
- Acting on dangerous impulses (p. 2).

4.4. Pharmaceutical company responses

As of November 14, 2004 when this author downloaded information from Prozac.com, Zoloft.com and Paxil.com, none of the information provided by the companies had been updated to meet the new FDA standards. The following information concerning suicide was provided on Prozac: "In addition, patients and their caregivers should be aware of the following information: Depression, as a disease, can be associated with periods when the symptoms can worsen and thoughts of suicide can emerge. Patients and their families should watch for these as well as for anxiety, agitation, panic, difficulty sleeping, irritability, hostility, aggressiveness, impulsivity, restlessness, or over excitement and hyperactivity. Call the doctor if any of these are severe or occur suddenly. Be especially observant at the initiation of antidepressant drug therapy and when there is a change in dose".

The above warning material is not contained in a black box and does not make clear that any of these adverse events are associated with the drug rather than with depression.

5. British regulatory actions

The British began investigating the risks of SSRIs in children before the FDA and helped to spur the American agency into action. After a series of investigations and reports, on December 10, 2003 the Medicines and Healthcare Products Regulatory Agency (MHRA) issued an "Urgent Message" to healthcare providers that gave a "summary of advice" stating "Paroxetine, venlafaxine, sertraline, citalopram and escitalopram are now contraindicated in pediatric MDD in the under 18s" [31]. The MHRA concluded that the "risk/benefit balance is unfavourable" for children for all of the newer antidepressants except Prozac. (Contrary to the MHRA, the FDA found an increased rate of suicidality for Prozac.) The MHRA did find an increased rate of mania and hypomania in children compared to adults for Prozac but not self-harm or suicidal thoughts. For sertraline it found increased rates of agitation, anorexia, insomnia and suicidal thoughts and self-harm. For citalopram, paroxetine and venlafaxine it found increased rates of self-harm and for escitalopram and fluvoxamine it found no data from clinical trials.

A contraindication for children means that the drug should not be given to them. The FDA has the power to label the antidepressants contraindicated in children but failed to do so. Furthermore, the British did not add to warnings concerning these drugs for adults.

One year later on December 6, 2004 the MHRA published its conclusions, a Dear Doctor letter, and new warnings for SSRIs. The MHRA continued to warn about SSRI-induced suicidality in children under eighteen. In its new warnings entitled "Suicidal Thoughts/Behaviour" the agency required the following warning [32] "The use of [any SSRI] has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often unaccompanied by an inability to sit or stand still" (p. 1).

The MHRA also published the "Report of the Focus Group" of the Committee on Safety of Medicines (CSM) [22]. As a discussion point, the focus group noted in parentheses, "Members of the group commented that suicidal ideation and akathisia can happen within a short time of initiating treatment, with a sudden change in dose, or as a consequence of missing a dose or on drug withdrawal". (This author has evaluated cases of akathisia and agitation in association with violence or suicide occurring under all four of these listed drug conditions: at the start of treatment, at dose changes, after a missed dose, and during withdrawal.)

Ultimately the British agency concluded that all the SSRIs except Prozac are ineffective in children and that all (including Prozac) pose some risk of causing suicidality. It banned the use of all SSRIs except Prozac in children under age eighteen [31,32].

6. Canadian regulatory actions

On June 3, 2004, before the FDA issued its formal label changes, Health Canada (the Canadian drug regulatory agency) issued an Advisory: "Health Canada advises Canadians of stronger warnings for SSRIs and other newer antidepressants"[5] [19].

The advisory made a broader warning than the later U.S. version: "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 and warned about both harm to self (suicide) and harm to others (violence).

The advisory described the stimulant syndrome and related it to suicide (harm to self) and violence (harm to others): "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.)

The advisory encouraged awareness of the whole range of stimulant-like or activation symptoms for all age groups: "Doctors are advised to carefully monitor patients of all ages for emotional or behavioural changes that may indicate potential for harm, including suicidal thoughts and the onset or worsening of agitation-type adverse events".

After consultations with Health Canada, Pfizer upgraded its warnings for Zoloft (sertraline) on May 26, 2004 [36]. In a black boxed warning under the rubric "Adult and Pediatrics: Additional data", the new warnings contain some of the basic material in the subsequently published Advisory from Health Canada, including the risk of both suicide and violence in children and adults: "There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. 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".

The warning specified, "Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behavior is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes".

[5]The drugs addressed by Health Canada were bupropion (Wellbutrin and Zyban), citalopram (Celexa), Fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), Paroxetine (Paxil), sertraline (Zoloft) and venlaflaxine (Effexor).

The list of adverse reactions – "akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization" – once again underscores the potential risk of violence. The term "disinhibition" does not appear in the FDA lists of adverse effects but is encompassed by several FDA terms such as irritability, agitation, and impulsivity. All of these symptoms are commonly seen in association with violence.

7. Discussion

7.1. Earlier documentation of the antidepressant-induced stimulant syndrome, violence and suicide

Evidence for the capacity of the newer antidepressants to produce stimulation with violence against self and others has been accumulating for more than a decade and has been reviewed recently by this author [6]. The evolution of the author's concept of antidepressant-induced activation or stimulation has been documented since 1992 [2–4,7,9]. Shortly before the FDA hearings, this author summarized [6]: "Mania with psychosis is the extreme end of a stimulant continuum that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progresses toward more severe agitation, aggression, and varying degrees of mania" (p. 32).

The FDA and Health Canada confirmed my observations when they used almost identical language in their recent warnings about the risks associated with the newer antidepressants.

7.2. Stimulation as a cause of suicidality and violence

There are at least four stimulant-like syndromes that can lead to violence and suicide [6]:

1. The production of a *stimulant continuum* that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progresses toward more severe agitation, aggression, and varying degrees of mania. Mania or manic-like symptoms include disinhibition, grandiosity, sleep disturbances, and out-of-control aggressive behavior, including cycling into depression and suicidality.
2. The production of a combined state of *stimulation and depression* – an *agitated depression* – with a high risk of suicide and violence. Often the overall depression is markedly worsened.
3. The production of *obsessive preoccupations* with aggression against self or others, often accompanied by a worsening of any pre-existing depression.
4. The production of *akathisia,* an inner agitation or jitteriness that is usually (but not always) accompanied by an inability to stop moving. It is sometimes described as psychomotor agitation or restless leg syndrome. The state causes heightened irritability and frustration with aggression against self or others, and often a generally worsening of the mental condition (p. 46).

7.3. Criteria for the diagnosing SSRI-induced violence confirmed by FDA

Based on clinical and forensic experience and research studies, the conditions can be defined under which SSRI-induced suicide and violence can be diagnosed [6]. Although most cases will not display all of the criteria, most cases will display one or more of them. As annotated in the following list, the recent FDA and Canadian warnings confirm the essentials of these earlier observations:

1. A relatively sudden onset and rapid escalation of the compulsive aggression against self and/or others.

- Confirmed in the FDA label's mention of drug-induced increased depression or suicidality "especially if these symptoms are severe, abrupt in onset . . ."

2. A recent (typically within two months) initial exposure to the medication, or a recent change in the dose of the medication, or a recent addition or removal of another psychoactive substance to the regimen.
   - Confirmed by the FDA label update note that suicidality occurs "especially early during antidepressant treatment and when the dose is adjusted up or down".
3. The presence of other adverse drug reactions, often involving akathisia or stimulation along a continuum from irritability and agitation to agitated depression and mania.
   - Confirmed by the FDA's listing of these events in the label, including akathisia, irritability, agitation, and mania.
   - Confirmed by Health Canada linking stimulant effects to the production of harm against self and others in children and adults.
4. Resolution of the syndrome after termination of the causative medication, often with a marked overall improvement in the individual's mental status.
   - Not addressed by the FDA.
5. An extremely violent and/or bizarre quality to the thoughts and actions.
   - Partially confirmed by the FDA's warning to be alert for antidepressant adverse reactions "especially if they are severe".
6. An obsessive, compelling, unrelenting quality to the thoughts and actions.
   - Not addressed by the FDA.
7. An out-of-character quality for the individual as determined by the individual's history.
   - Confirmed by the FDA label mention of "unusual changes in behavior" and new symptoms that "were not part of the patient's presenting symptoms".
8. An alien or ego-dystonic quality as determined by the individual's subjective report.
   - Not addressed by the FDA.

8. Conclusion

In 2004, drug regulatory agencies in the United States (FDA), Canada (Health Canada) and Great Britain (MHRA) addressed the issue of antidepressant-induced suicidality in the pediatric population (under age 18). All three agencies confirmed that the new antidepressants cause suicidality in children and adolescents, and issued warnings to the public and healthcare professionals. The MHRA banned the use of the newer antidepressants (except Prozac) in children.

The FDA focused on the SSRIs fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escilalopram (Lexapro), as well as venlafaxine (Effexor), mirtazapine (Remeron), Wellbutrin or Zyban (bupropion) and nefazodone (Serzone). The American agency required a black box warning concerning suicidality in children and additional warnings concerning

stimulation effects in children and adults, including hostility and aggression. The agency published its "FDA Proposed Medication Guide: About Using Antidepressants in Children and Adults" in which it warned about patients showing signs of violence on antidepressants, including "new or worse irritability", "acting aggressive, being angry, or violent" and "acting on dangerous impulses".

Health Canada warned that antidepressants cause stimulation or activation in children and adults, including a variety of adverse events related to violence, such as agitation, irritability, dyscontrol, hostility, aggression, and mania. Health Canada warned about the risk of harm to self and others in children and adults.

In conclusion, clinicians need to give greater attention to antidepressant-induced activation (stimulation) that can result in both suicidal and violent acts in children and adults.

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