

Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis *

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Abstract. Evidence from many sources confirms that selective serotonin reuptake inhibitors (SSRIs) commonly cause or exacerbate a wide range of abnormal mental and behavioral conditions. These adverse drug reactions include the following overlapping clinical phenomena: a stimulant profile that ranges from mild agitation to manic psychoses, agitated depression, obsessive preoccupations that are alien or uncharacteristic of the individual, and akathisia. Each of these reactions can worsen the individual's mental condition and can result in suicidality, violence, and other forms of extreme abnormal behavior. Evidence for these reactions is found in clinical reports, controlled clinical trials, and epidemiological studies in children and adults. Recognition of these adverse drug reactions and withdrawal from the offending drugs can prevent misdiagnosis and the worsening of potentially severe iatrogenic disorders. These findings also have forensic application in criminal, malpractice, and product liability cases.

1. Introduction

Soon after the introduction of the first selective serotonin reuptake inhibitor (SSRI), fluoxetine (Prozac) into the United States marketplace in January 1988, reports began to appear describing fluoxetine-induced violence against self and others. In May 1990 the U.S. Food and Drug Administration required the manufacturer of Prozac, Eli Lilly and Company, to add "suicidal ideation" and "violent behaviors" to the *Postintroduction Reports* section of its label.¹ In 2003 the British Committee on the Safety of Medicines and the U.S. Food and Drug Administration issued warnings about increased rates of self-harm and suicidal behavior in children and youth under the age of 18 exposed to paroxetine (Paxil) [78]. Most recently, on August 22, 2003, the manufacturer of venlafaxine (Effexor) issued a similar "Dear Doctor" letter warning about the increased risk of "hostility and suicide-related adverse events, such as suicidal ideation and self-harm" in children age 6 to seventeen [79].

In August 11, 1990, an editorial in *The Lancet* [53] included "the promotion of suicidal thoughts and behaviour" (p. 346) among the adverse effects of fluoxetine. The following year, the *British National Formulary*, a joint publication of the British Medical Association and the Royal Pharmaceutical Society (1991), listed suicidal ideation and violent behavior as fluoxetine side effects. Subsequently, many books and reports have dealt with the subject of SSRI-induced violence and suicide (e.g., [10,12,14,35,40,72]).

This report will provide an extensive review and analyze the literature concerning SSRI-induced suicide and violence, and identify several clinical syndromes that can cause the phenomena. It will examine

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¹The section that lists violence and suicide as possible adverse drug reactions begins with a caveat that the reported reactions "may have no causal relationship with the drug."

the clinical and forensic implications of these findings, and also examine the ethical and scientific controversy surrounding the capacity of psychoactive agents to cause “bad behavior.” (The subject of abnormal behavior induced by *withdrawal* from SSRIs will be considered in a later publication. Also see [15]).

2. The class of SSRIs

These selective serotonin reuptake inhibitors (SSRIs) include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and, most recently, escitalopram (Lexapro). These drugs block the removal of the neurotransmitter serotonin from the synaptic cleft. A number of other antidepressants are potent non-selective serotonin reuptake inhibitors (NSRIs). These include the atypicals venlafaxine (Effexor) and nefazodone (Serzone) and the tricyclic clomipramine (Anafranil).

When observations are made in clinical practice and in the scientific literature concerning the impact of SSRIs, they are typically treated as a single category or class of pharmacological agents. It is generally recognized that an adverse mental or behavioral reaction, such as agitation or mania, that is observed in regard to one SSRI is likely to be found with all the other SSRIs.² While usually examined as separate classes of antidepressants, the NSRIs also share many characteristics with the SSRIs, including the capacity to induce stimulation, anxiety, agitation, and mania.

3. SSRI-induced mania and the continuum of stimulation

All antidepressants cause mania and mania is an acknowledged adverse effect in the FDA-approved label of all antidepressants. Preda et al. [66] carried out a retrospective study of 533 psychiatric hospital admissions over a fourteen month period and found that 43 (8.1%) could be attributed to antidepressant-induced mania and/or psychosis. The percentages for each antidepressant were as follows: the SSRIs (70%), the newer atypicals (venlafaxine, nefazodone, and bupropion) (21%), and the older tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline) (21%). The total percentage exceeded 100% because of overlapping medications in five cases. Twelve of the cases represented new-onset mania or psychosis. The three illustrative cases were severe, including two with marked suicidal potential. A 52-year-old married woman with a past history of bipolar disorder developed “command auditory hallucinations with suicidal content” while taking desipramine and fluvoxamine, as well as risperidone, zolpidem, and oxazepam (p. 31). A 42-year-old woman with a one-year history of depression “began to experience derogatory and then command auditory hallucinations to kill herself” while on fluoxetine as well as lithium and thioridazine (p. 31). Finally, a 49-year-old woman taking venlafaxine for “low mood and anxiety” developed symptoms of paranoia, feelings of doom, and a delusion that television messages were being directed at her (p. 31). All three patients improved rapidly with treatment that included termination of the antidepressants.

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. At the lower end of the continuum, an ordinarily shy

²Marangell, Yudofsky and Silver [58] observed, “All SSRIs have a similar spectrum of efficacy and a similar side-effect profile” (p. 1035). In the same vein, Borg and Brodin [6] remarked, “There seems to be little difference between the SSRIs with respect to frequency and severity of adverse effects” (p. 66) and Grimsley and Jann [37] concluded, “Overall, the adverse-effect profiles of the different SSRIs are comparable” (p. 938).

Table 1

Mental and behavioral Adverse Drug Reactions (ADRs) in adults caused by paroxetine from the 2001 FDA-approved label for Paxil

Frequent ^a	Infrequent ^b
Mania/Hypomania 2.2% of bipolar patients	Paranoid reaction
Mania/Hypomania 1% of depressed patients	Psychosis
Insomnia 13%	Hostility
Nervousness 5%	Euphoria
Anxiety 5%	Delirium
Agitation 1%	Hallucinations
Drugged feeling 2%	Abnormal thinking
Confusion 1%	Depersonalization
Central nervous system stimulation	Neurosis
Emotional lability	Lack of emotion
Concentration impaired	Libido increased
Amnesia	
Depression	
Tremor 8%	
Sweating 11%	
Palpitation 3%	

^aFrequent means at a rate of 1% or greater.

^bInfrequent means at a rate between 1% and 0.1%. All 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 Paxil, including 6,145 depressed patients. Table compiled from the label by Peter R. Breggin.

young woman acted silly and more outgoing on fluoxetine, and then developed suicidal feelings when she missed doses [8]. Evidence for this stimulant continuum or syndrome of SSRI-induced adverse reactions will be found in many of the following reports. Sometimes the psychoses lack manic qualities and appear more paranoid in nature.

SSRI labels tend to be organized in ways that avoid any implication that the medications can cause stimulation; but detailed analyses of the labels disclose that these drugs produce a continuum of stimulation (Breggin [13] for an analysis of the Luvox label; Breggin and Breggin [14] for an analysis of the Prozac label). Table 1 was compiled to illustrate the spectrum of SSRI-induced adverse drug reactions and illustrate the frequency of stimulant-like effects. All of the effects listed in the table can occur with stimulants such as amphetamine and cocaine, and many are typical of these stimulants, including hypomania/mania, insomnia, nervousness, anxiety, agitation, central nervous system stimulation, emotional lability, tremor, sweating, and palpitation, as well as paranoid reaction, psychosis, hostility, and euphoria.

Confirmation of the stimulant syndrome was provided in a previously undisclosed internal document from Eli Lilly and Company, the manufacturer of Prozac (fluoxetine) that was obtained during discovery in product liability suits against the company (Beasley [5]; discussed in Breggin [10, pp. 87–88]; Breggin [9], Fentress Trial Exhibit [28]). Charles Beasley of the company's Division of Clinical Neurosciences evaluated what he called "activation" in patients taking fluoxetine or placebo in the controlled clinical trials used for Food and Drug Administration (FDA) approval of Prozac for depression. Beasley defined activation as including any of the following: nervousness, anxiety, agitation, insomnia. Beasley found that 38% of fluoxetine-treated patients developed "activation," but only 19% of placebo patients. The

proportion of patients “activated” by fluoxetine would have been higher if other expressions of stimulation had been included, such as akathisia, hyperactivity, euphoria, and mania. It would have been further increased if many of the patients had not been prescribed sedative tranquilizers to quiet their symptoms of stimulation [14].

Reports authored by Kapit [47,48], the FDA official in charge of evaluating adverse drug effects during the approval process of Prozac for depression, repeatedly warned that fluoxetine has a stimulant profile similar to amphetamines. He was concerned that stimulant effects such as insomnia, nervousness, anorexia, and weight loss would produce agitated depression and worsen the condition of some depressed patients (unpublished data discussed and quoted in Breggin [10, pp. 79–81]).³

Clinically, agitated depression is an unstable condition that can lead to violence against self or others more frequently than a non-agitated depression. A number of reports cited in the following sections will mention agitation in patients who behave abnormally as a result of antidepressant effects.

4. Case studies related to SSRI-induced suicidality, violence, and extreme abnormal behavior in adults

4.1. Case reports of mania, violence, and suicide

There are many case reports in the scientific literature documenting the capacity of SSRIs to cause mania in adults, often in association with irritability and aggression. Christensen [18], for example, reported on the case of 32-year-old man who developed his first manic episode while taking paroxetine. He became psychotic and “threatened his parents with physical harm” (p. 1400). Other reports cite fluvoxamine as the causative agent (e.g., [17,24,61]).

Dorevitch et al. [24] described three cases of fluvoxamine-induced mania. Each case was recognized quickly and the drug was reduced in dose or stopped so that potentially disastrous outcomes were avoided. Had the patients been more secretive or the monitoring less effective, the results could have been more drastic in outcome. In the first case, the patient developed a psychotic manic state with auditory hallucinations. In the second case, the patient became euphoric, displayed increased energy, inappropriate behavior with sexual advances toward other patients, irritability, and fears that people were out to kill him. In the third case, the patient developed multiple signs of mania from excessive sexual activities to excessive talking and argumentativeness. Manic patients who are “argumentative” can sometimes become very aggressive when thwarted.

Okada and Okajima [61] described three cases of aggressive and violent behavior induced by fluvoxamine. On 150 mg per day, a 32-year-old woman became both irritable and aggressive, and she expressed impulsive violence during arguments with her family. She improved after her fluvoxamine was reduced (but not stopped). Paroxetine with its high impact and short duration of action is more like fluvoxamine than like fluoxetine. A 29-year old woman on 150 mg of fluvoxamine daily became nervous and irritable and then impulsively violent and was admitted to a psychiatric hospital. She improved with discontinuation of the drug and further treatment with other medications. A 28-year-old woman receiving 150 mg of fluvoxamine daily exhibited signs of irritability and aggressive behavior and expressed violence

³In a discussion of similarities among SSRIs (in Leonard [55, pp. 9–10]), J. Mendlewicz points out that animal studies indicate that some SSRIs can cause “alertness, agitation or anxiety, or interfere with the quality of sleep” and he asks, “Are there differences between SSRIs in terms of these early ‘activating’ effects?” B.E. Leonard answers that there no known differences among the SSRIs in this regard to their capacity to induce “anxiety or agitation.”

toward her mother. She improved when the fluvoxamine was stopped and other medications instituted. The authors warned about the existence of impulsive and aggressive behavior induced by fluvoxamine.

In another case report, a woman taking fluvoxamine became suicidal and had to be hospitalized [4]. In the hospital the fluvoxamine dose was increased from 50 mg per day to 150 mg per day whereupon her condition worsened and she began to experience auditory hallucinations. The fluvoxamine was discontinued and she recovered within twenty-four hours, confirming that the medication had caused the depression and psychosis.

4.2. Case reports of SSRI-induced akathisia and aggression

Akathisia is a painful inner agitation that typically manifests as the inability to sit still or to stop moving. The hyperactivity may manifest itself subtly as a feeling of jitteriness or grossly as frantic pacing or repeatedly sitting up and down. The inner agitation associated with akathisia can become extremely uncomfortable, causing the individual to feel tortured from within (see vivid descriptions in Van Putten [74,75] and Breggin [10], leading to extreme irritability and suicide or violence.

Although akathisia by definition usually involves a hyperactive movement component, clinical experience indicates that the same jittery, agitated subjective experience, accompanied by irritable, violence or suicidal feelings, can occur without the specific component of feeling driven to move about. Indeed, on earlier occasions, the individual may have experienced the associated compulsion toward hyperactivity. Healy [41] made similar observations. Furthermore the *Diagnostic and Statistical Manual of Mental Disorders* [3] specifically allows for an alternative diagnosis of “acute akathisia with only subjective or only objective complaints, but not both” (p. 801).

Lipinski et al. [57] reported on five cases of akathisia caused by fluoxetine. They also reviewed the literature and found rates of 9.7% to 25% for fluoxetine-induced akathisia. They concluded, “In summary, fluoxetine, and perhaps other antidepressant drugs as well, may produce the side effect of akathisia fairly frequently” (p. 342). The Public Citizen Health Research Group [67] estimated a rate of 15–25%. While studies of SSRI-induced akathisia vary greatly in the frequency with which this disorder is observed, they confirm that it is common.

Lane [54] observed, “SSRI-induced akathisia may represent a form of serotonergic overstimulation or serotonin toxicity” (p. 203). He also cited research linking the phenomenon to the impact of SSRIs on the dopaminergic system. He warned, “The emergence of symptoms of akathisia could be mistaken for a worsening of depression, especially the conversion of a non-agitated depression to an agitated form” (p. 206). This error in judgment could lead to the prescription of increased doses of the offending medication, resulting in a severely worsened condition. Lane cited studies indicating that “fluoxetine is not an appropriate choice of antidepressant for depressed patients with agitation and restlessness” (p. 206) because it can lead to increased rates of agitation, anxiety and manic reactions.

Rothschild and Locke [69] reported on three cases of fluoxetine-induced suicidality associated with akathisia. Each case of suicidality developed on fluoxetine (challenge) and then resolved when the drug was stopped (dechallenge). The suicidality then returned when the drug was started a second time (rechallenge) and stopped again when the drug was stopped (a second dechallenge). During rechallenge each of the patients developed akathisia and reported that this feeling had caused them to become suicidal each time.

Wirshing et al. [77] reported on five cases of a fluoxetine-induced syndrome consisting of akathisia and suicidality. In all five cases, the akathisia and the suicidality remitted when the drug was stopped or reduced in dosage. In one case, a rechallenge with an increased dose of fluoxetine again produced

the syndrome. They concluded, “Our cases appear to confirm that certain subjects experience akathisia while taking fluoxetine and that this effect is dose-related in the individual patient. . . . Furthermore, like the akathisia in the neuroleptic-treated schizophrenic population, ‘fluoxetine akathisia’ can apparently be associated with suicidal ideation, sometimes of a ruminative intensity” (p. 581).

Masand et al. [59] reported on two cases of suicidality in association with fluoxetine. One of the patients suffered from akathisia. In both cases, the suicidal feelings subsided shortly after stopping the medication. Neither patient had prior suicidal ideation. Both developed violent fantasies (hanging and jumping out a window).

Akathisia will also be found in combination with SSRI-induced mania and aggression (see below).

4.3. Case reports of SSRI-induced obsessive suicidality and aggression

A number of clinical reports have described a syndrome of obsessive SSRI-induced suicidality and aggression that seems particular to these drugs. The characteristics were first described in a report on fluoxetine-induced obsessive suicidality by Teicher et al. [71]. They summarized, “Six depressed patients free of recent serious suicidal ideation developed intense, violent suicidal preoccupation after 2–7 weeks of fluoxetine treatment” (p. 207). Additional cases and potential mechanisms of action were analyzed by Teicher et al. [72].

Dasgupta [21] described a similar case of “intense suicidal preoccupation” (p. 1570) after four weeks of fluoxetine treatment in a woman who had not been previously suicidal. She, too, rapidly recovered on stopping the fluoxetine. The syndrome was also described by Rothschild and Locke [69] in three patients taking fluoxetine, each of whom again reacted with suicidality when rechallenged by a second administration of fluoxetine. Hoover [43] described another similar case who developed intense, violent suicidality on the two occasions that she was exposed to fluoxetine.

Creaney et al. [20] described two patients who became suicidal on SSRIs. One patient developed dysphoria and manic symptoms on fluoxetine and then developed a similar syndrome, this time with suicidal feelings, on fluvoxamine. Another patient became intensely and violently suicidal sixteen days after starting fluoxetine.

Gualtieri [38] described the “case of a mentally handicapped gentleman whose rates of self-injurious behavior doubled on fluoxetine, and then fell to baseline after the drug was withdrawn” (p. 393). Gualtieri pointed out that fluoxetine can cause apathy and indifference in some patients and, conversely, mania in others.

Based on the literature and my clinical experience, the syndrome of SSRI-induced obsessive suicidality and violence includes many and sometimes all of the following:

1. A relatively sudden onset and rapid escalation of the compulsive aggression against self and/or others.
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.
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.
4. Resolution of the syndrome after termination of the causative medication, often with a marked overall improvement in the individual’s mental status.
5. An extremely violent and/or bizarre quality to the thoughts and actions.
6. An obsessive, compelling, unrelenting quality to the thoughts and actions.

7. An out-of-character quality for the individual as determined by the individual's history.
8. An alien or ego-dystonic quality as determined by the individual's subjective report.

5. Epidemiological studies and clinical trials related to SSRI-induced, depression, suicidality, violence, and extreme abnormal behavior in adults

5.1. Epidemiological studies and clinical trials of SSRI-induced mania and aggression

The following studies focus on SSRI-induced manic-like symptoms and mania. The clinical syndrome of mania is commonly associated with increased irritability, aggressiveness, physical violence, and a variety of antisocial and criminal behaviors ([3, pp. 357–362]). However, as the following review indicates, many patients will switch from mania to depression and suicidality.

As documented in the FDA-approved labels for SSRIs, clinical studies conducted for the FDA-approval process have shown increased rates of mania. For example, even in the relatively short four-to-six week trials used for the approval of Prozac for depression, slightly more than 1% of patients developed hypomania and mania (see, for example, the 1990 label for Prozac for depression). An unpublished FDA report obtained through the Freedom of Information Act indicated that fluoxetine caused mania at a three times greater rate than tricyclic antidepressants given in the same studies (Kapit [48]; reviewed in Breggin [10, p. 86]). Furthermore, in 23 of the 33 cases, fluoxetine caused mania in patients with no past history of mania. In no cases did the older antidepressants cause mania in patients with no prior history. This data contradicts the commonly held clinical notion that SSRI-induced mania is limited to patients with an underlying bipolar disorder.

Howland [44] found 11 cases of SSRI-induced mania among approximately 184 (6%) patients treated at a university clinic and hospital with a variety of SSRIs, including fluoxetine, paroxetine, and sertraline. The episodes were “generally quite severe” (p. 426). Eight of the 11 patients became psychotic and 4 were so agitated that they had to be put in seclusion, even though they were probably receiving additional medication to control their iatrogenic mania.

Ebert et al. [26] attempted to develop a rate for severe mental aberrations caused by fluvoxamine. They carried out a prospective study of 200 inpatients over a total of 8200 treatment days with the SSRI. Fourteen patients (17%) developed hypomania according to DSM-IV criteria. Three patients (1.5%) developed insomnia, agitation, confusion and incoherent thoughts. These patients became potentially violent and suicidal. One, a 35-year old man, developed agitation and restless legs that progressed to insomnia, confusion, paranoid ideas, and hallucinations. He recovered after fluvoxamine was stopped. Another patient, a 38-year old man, developed psychomotor agitation with insomnia that progressed to aggressiveness, incoherent thoughts, confusion, auditory hallucinations and paranoid ideas. He also recovered when fluvoxamine was stopped. A third patient, another 35-year-old man, developed insomnia and then became agitated with restless legs, and severely depressed with suicidal ideas. He was also incoherent, and confused with paranoid ideas. He too recovered within a few days after stopping the medication. Based on the clinical descriptions, all three patients probably suffered from akathisia.

Ebert and his colleagues [26] summarized the syndrome as consisting of insomnia, confusion, incoherent thoughts, agitation, hallucinations and paranoid ideas. They observed that it was especially frequent in combination with other drugs. They considered it rare but their data indicate that it was common.

Adding up the 14 hypomanic patients and the 3 psychotic and aggressive patients, there were at least 17 severe central nervous system (psychological) reactions among 200 patients for a rate of 8.5%.⁴

Peyre et al. (1992) reviewed the histories of 189 patients treated with fluvoxamine and found a rate of 2.5% for manic switches, i.e., the development of mania during treatment for major depression.

Troisi et al. [73] used 20 mg per day of fluoxetine to treat nineteen retarded inpatients with epilepsy and a current or recent history of aggressive behavior. All of them were taking other medications as well. Using a standardized rating scale for assessing behavior before, during, and after treatment with fluoxetine, they found an increase in aggressive behavior in nine patients. Unexpectedly, the behavior decreased to *below* pre-treatment levels after the withdrawal of the fluoxetine. The authors conclude that fluoxetine can worsen aggression in retarded patients with impulsive aggressive behavior.

The FDA conducted an epidemiological study comparing fluoxetine to trazodone in regard to spontaneous reports concerning hostility and intentional injury (Food and Drug Administration [31]). When the FDA factored in the greater number of prescriptions for fluoxetine, fluoxetine still had a higher frequency of reports for aggressive and violent behavior. Furthermore, the reports began to accumulate before the controversy surrounding fluoxetine and violence (suppression of the data discussed in Breggin [10, pp. 88–89]).

5.2. *Epidemiological studies and clinical trials of SSRI-induced depression and suicidality*

An unpublished document obtained during discovery in product liability suits against the drug company disclosed that Eli Lilly and Co., the manufacturer of Prozac (fluoxetine), had evaluated the comparative rates of suicide attempts on fluoxetine, amitriptyline and placebo. The data was generated during controlled clinical trials conducted for the FDA-approval process for Prozac for depression. Based on the company's data for controlled clinical trials, patients taking fluoxetine were three-to-six times more likely to attempt suicide than a similar group of patients taking older antidepressants or placebos (see my testimony in Breggin [9]; reviewed in Breggin [10, pp. 89–91]). An evaluation by a consultant to the company, Avery Winokur, concluded that the increased rate might be due to fluoxetine-induced overstimulation of the depressed patients (unpublished documents reviewed in Breggin [10, pp. 89 ff]; also see Breggin [9]).

Healy [39] reviewed and reanalyzed data comparing the number of suicides and suicide attempts per patient in worldwide placebo controlled clinical trials used for the FDA antidepressant approval process (Khan et al. [49] and Khan et al. [50]). The drugs included four SSRIs (sertraline, paroxetine, citalopram, and fluoxetine). As a percentage of patient numbers, there was a statistically significant difference between combined suicides and suicide attempts among all SSRIs patients (1.55%) and among all SSRI trial placebo patients (0.48%). There were also a significantly greater number of completed suicides on SSRIs in the combined suicide and suicide attempt group, as well as in the paroxetine group individually, compared to placebo.

Donovan et al. [23] found a significantly increased rate of completed suicide among patients treated with SSRIs compared to those treated with tricyclic and other antidepressants. After correcting the data for the number of prescriptions for each drug, SSRIs were 3.5 times more likely to be associated with suicide. The study was conducted in three regions of England and Ireland, and involved 222 suicides.

Donovan et al. [22] also conducted a prospective study of 2776 consecutive cases of deliberate self-harm age seventeen and older who were seen at the accident and emergency department of Derbyshire

⁴According to the FDA, an adverse drug reaction rate of 1% is frequent or common.

Royal Infirmary as a consequence of any act of deliberate self-harm during a two year period (1995–1996). Of the 2776 cases, 307 had received an antidepressant 30 days or less prior to the incident of deliberate self-harm. With the rate of prescribing in Derbyshire taken into account, 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 the tricyclics amitriptyline, dothiepin and imipramine. The relative incidence of deliberate self-harm per 10,000 prescriptions was broken down in a table as follows: fluoxetine (19.8), sertraline (14.8), paroxetine (12.1), all SSRIs (16.6), imipramine (3.5), amitriptyline (3.0), and all tricyclics (5.6). Compared to amitriptyline, the relative risk for all SSRIs was many times higher: fluoxetine (6.6), sertraline (4.9), paroxetine (4.0), and all SSRIs (5.5). Of interest in regard to causation, the risk for the tricyclic clomipramine was very high as well with a relative incidence of 13.8 and a relative risk compared to amitriptyline of 4.6. Among the tricyclics, clomipramine has the strongest inhibitory effect on serotonin reuptake (see, for example, *Drug Facts and Comparisons* [25]).

Jick et al. [46] conducted an epidemiological study of reports from general practices (primary care) in the United Kingdom involving 172,598 patients who had at least one prescription for one of ten antidepressants. Rates of suicides were compared for patients on the various antidepressants. Patients taking fluoxetine were twice as likely to commit suicide compared to patients on other antidepressants. In comparison to three more sedating antidepressants – doxepin, imipramine, and amitriptyline – fluoxetine was four times more likely to be associated with suicide. Taking into account a past history of suicidal behavior and/or antidepressant treatment, fluoxetine remained twice as likely to be associated with suicide. Nonetheless, the authors attempted to explain away the dramatic differences.

Fisher et al. [29] conducted a phone survey of pharmacy patients taking various antidepressants and found a higher rate of suicidality on SSRIs. In a related study, Fisher et al. [30] 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).

Muijen et al. [60] conducted a six-week double-blind study comparing fluoxetine, mianserin, and placebo with 26, 27, and 28 starters respectively, and 14, 14, and 16 finishers respectively. Two of the fluoxetine patients “took an overdose within two weeks of starting the study, and in both cases this was related to a deteriorating clinical state that necessitated hospitalization” (p. 386). None of the patients in the other drug group or the placebo group suffered from this decline and suicidality. Remarkably, the authors do not include these reactions among the adverse drug effects.

Gorman et al. [36] conducted an open trial of fluoxetine involving sixteen patients with panic disorder. They reported, “Two of the nonresponders became depressed and had suicidal ideation while taking fluoxetine. Only one of the two had a history of depression” (p. 331). The authors did not comment on this finding.

Healy [40] conducted a randomized double-blind crossover study comparing the effects of sertraline 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. Case A, a 30-year-old woman, became withdrawn and ruminated over impulsive, disinhibited actions. She was also tearful and did not feel like herself. In addition, her diary recorded impulsiveness, irritability, over-sensitivity, and marked suspicion. She became obsessed with killing herself and almost threw herself beneath a car or train. Case B, an otherwise peaceful 28-year old woman, experienced severe road rage and actually grabbed a teenage boy and threatened to knock him down. On the SSRI,

she felt aggressive and fearless. While emotionally disturbed and out-of-control (disinhibited), the two individuals nonetheless felt and appeared emotionally blunted.

The mixture of apathy and disinhibited aggressiveness reported by Healy is probably a common finding in patients who act uncharacteristically violent as a result of taking SSRIs. Hoehn-Saric et al. [42] reported on "Apathy and Indifference in Patients on Fluvoxamine and Fluoxetine." They described apathy, indifference, loss of initiative and disinhibition with and without hypomania in five patients.

Levine et al. [56] reported that 7% of 59 non-depressed obese patients became depressed following a rapid increase in fluoxetine to a dose of 80 mg per day.

5.3. *Coroner studies*

Frankenfield et al. [33] conducted a retrospective case review of all deaths in Maryland where either fluoxetine or tricyclic antidepressants was forensically detected. The study covered a three and one-half year period of time. They found a statistically significant increase in *violent* suicides in association with fluoxetine (65% versus 23%). Violence was defined to include "gunshot or shotgun wounds, suffocation, stabbing, strangulation, drowning, falls and jumping in front of a moving vehicle" (p. 109). The evaluation of the suicide attempts were blind to which medications were involved.

Bost and Kemp [7] reviewed a series of coroner's reports in Dallas, Texas, involving fifteen suicides associated with fluoxetine treatment. The study covered a nine month period. While they appreciated that their data was impressionistic, they warned that the proportion taking fluoxetine and committing suicide was high enough to be of concern to health care providers.

6. **Studies related to SSRI-induced suicidality, violence, and extreme abnormal behavior in children**

Many cases of SSRI-induced violent or suicidal behavior involve children or young adults. However, even in regard to cases involving older persons, the literature on children and youth is important. Adverse behavioral effects tend to show up more frequently and severely in children, providing a magnified view of the same or similar effects that the drugs are causing on adults.

6.1. *Clinical case studies involving children*

A single case study involving paroxetine described a sixteen-year-old who became manic with angry outbursts after three weeks on the drug [62]. In another single case study, a 17-year-old mildly retarded youngster was started on fluvoxamine 50 mg when he became depressed and anxious [70]. After a single dose, he developed increasing agitation and insomnia, followed in the next 24 hours by auditory and visual hallucinations, a fearful mood, and paranoid delusions about the devil. He required hospitalization and was treated with an antipsychotic drug. The authors believe that fluvoxamine caused the acute psychosis. As a third example of single case clinical reports, Wilkinson [76] described a character change with increased aggression in a fifteen-year-old boy taking fluoxetine. Uncharacteristically, he struck another youngster in the face. Fluoxetine was stopped and within a week he was no longer aggressive. The author identified blunting rather than akathisia as the motivational state.

Koizumi [52] described a thirteen and one-half year old boy who developed manic symptoms on 40 mg per day of fluoxetine. These side effects disappeared when the dose was lowered to 15 mg per day. However, after fifteen months of fluoxetine treatment he then developed "explosive, angry outbursts over

minor matters, which was totally unlike him” (p. 695). He then experienced a “weird” and ego-alien voice telling him to kill himself. He recovered from these symptoms within ten days of stopping fluoxetine.

6.2. *Epidemiological studies and clinical trials involving children*

Numerous epidemiological and clinical study reports confirm that SSRIs cause suicidal, violent and manic behavior in children and youth.

Three controlled clinical trials conducted for the FDA-approval of paroxetine for children under age eighteen demonstrated a three times increased rate of self-harm and suicidal behavior in paroxetine-treated children compared to placebo. Based on this data in 2003 the British Committee on Medicines prohibited the use of paroxetine in children and the U.S. Food and Drug Administration issued a warning [78].

The manufacturer of venlafaxine recently disclosed unpublished data from its controlled clinical trials for major depressive disorder [79]. Individuals below 18 years of age exposed to venlafaxine had more than twice the relative risk than those exposed to placebo in regard to the development of hostility (2% versus <1%) and suicidal ideation (2% versus 0%).

According to the FDA-approved label for fluvoxamine (Luvox in the *Physicians' Desk Reference* [64]), the SSRI causes a 4% rate of mania in children under age 18, compared to no cases of mania produced in a similar group of children on placebo. The rate was at least four times greater than in adults (see Breggin [13] for a more complete analysis of the Luvox label).

A controlled clinical trial found that fluoxetine caused a 6% rate of mania in depressed children and youngsters age 7–17 ([27, p. 1003]). The reactions were severe enough to cause the children to be dropped out of the trials. By contrast, none of the depressed youngsters on placebo developed mania.

Jain et al. [45] made a retrospective examination of the medical charts of children and young men age 8–19 who had taken fluoxetine in a university clinic setting. The researchers found that 23% of fluoxetine-treated young people developed mania or manic-like symptoms. Another 19% developed drug-induced hostility and aggression, including a grinding anger with short temper and increasing oppositionalism.

Constantino et al. [19] prospectively studied the course of aggressive behavior in nineteen SSRI-treated psychiatrically hospitalized adolescents who were not pre-selected for potential aggressiveness. They reported symptoms of aggression toward self or others in 12 of 19 patients on SSRIs. Of the 19 patients, 13 were assessed both on and off SSRIs. On the SSRIs there was increased verbal aggression ($P = 0.04$), increased physical aggression toward objects ($P = 0.05$), and increased physical aggression toward self ($P < 0.02$). No increase was observed in physical aggression toward others. The authors warned against using SSRIs to treat aggression in children.

Another study of children and youth age 8-16 in a university setting found that 50% developed two or more abnormal behavioral reactions to fluoxetine, including aggression, loss of impulse control, agitation, and manic-like symptoms [68]. The effects lasted until the fluvoxamine was stopped.

A second research study from the same university setting described a number of youngsters (6 of 42 or 14% in their cohort) who became aggressive and even violent while taking fluoxetine [51]. The researchers hypothesized that fluoxetine caused aggressive behavior by means of drug-induced activation (stimulation) or a specific serotonergic-mediated effect.

The report [51] provided a clinical window into the development of obsessive violence and a school-shooter mentality. A twelve-year-old boy on fluoxetine developed nightmares about becoming a school shooter and then began to lose track of reality concerning these events. This case occurred in a controlled-clinical trial and the investigators did not know that the child was getting fluoxetine until they broke the

double-blind code. The child's reaction occurred long before any of the well-known school shootings had taken place. Therefore, his reaction was not inspired by the school shootings; it was not a "copycat":

Thirty-eight days after beginning the protocol, F. experienced a violent nightmare about killing his classmates until he himself was shot. He awakened from it only with difficulty, and the dream continued to feel "very real." He reported having had several days of increasingly vivid "bad dreams" before this episode; these included images of killing himself and his parents dying. When he was seen later that day he was agitated and anxious, refused to go to school, and reported marked suicidal ideation that made him feel unsafe at home as well (p. 180).

The child was hospitalized first for three days and then for 17 days. He gradually improved. Then three weeks after his last hospitalization, his local physician – not one of the clinical investigators – put him back on fluoxetine. The child became acutely suicidal until the fluoxetine was stopped a second time.

This individual report is important for a variety of reasons:

- (1) It took place in a double-blind controlled clinical trial.
- (2) Entirely new symptoms related to violence developed on the drug (This stage is called challenge).
- (3) The symptoms terminated after stopping the drug (called dechallenge).
- (4) Some of the symptoms resumed on starting the drug again (called rechallenge).
- (5) The symptoms cleared for a second time after the drug was again stopped (demonstrating dechallenge for a second time).

7. Antidepressant-induced mania described in two standard sources

In a variety of forensic activities including criminal and civil cases, the courts sometimes rely on "authoritative" or "standard" texts in order to demonstrate that the opinions rendered are generally accepted by a significant portion of the medical or scientific community.

7.1. *The Diagnostic and Statistical Manual of Mental Disorders (1994, 2000)*

The American Psychiatric Association [2] *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* and the Fourth Edition Text Revision (*DSM-IV-TR*, [3]) are written by committees made up of professionals considered expert by many of their colleagues in their respective fields. The conclusions therefore provide a professional consensus or body of conventional wisdom in psychiatry that can at times be useful in clinical practice and in forensics. Many aspects of the *DSM-IV* are controversial. However, when such an essentially conservative consensus document provides evidence for SSRI-induced adverse reactions related to mania, suicide and violence, it should alert clinicians to the existence of these clinical phenomena and can provide an avenue for communicating in the courtroom concerning these risks.

The *DSM-IV* was published in 1994, several years after the advent of SSRI antidepressants and makes clear that all antidepressants can cause mania. The first SSRI, fluoxetine, was approved by the FDA in December 1987 and was in widespread use when the following observations about antidepressants were published in the manual.

DSM-IV makes multiple references to the fact that antidepressants can cause mania or manic-like behavior. It states, for example, "Symptoms like those seen in a Manic Episode may be due to the direct effects of antidepressant medication . . ." [2, p. 329]. Similarly, it observes, "Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication . . ." [2, p. 331].

References to antidepressant-induced mania and mood disorder can also be found elsewhere in the manual as well (e.g., pp. 332 [note at bottom of table], 334, 336, 337, 351, 371 and 372). *DSM-IV-TR* (2000) emphasizes that a diagnosis of mania or bipolar disorder should not be made when the hypomania or mania first appears while the individual is taking a medication that can cause these symptoms and “usually disappear when the individual is no longer exposed to the substance.” Of great clinical importance, it adds, “but resolution of symptoms can take weeks or months and may require treatment” (p. 191).

The association between mania and antisocial behavior, including violence, is underscored in the *DSM-IV*. Aggression is specifically mentioned as a feature of manic behavior. It is noted that “antisocial behaviors may accompany the Manic Episode,” “Ethical concerns may be disregarded even by those who are typically very conscientious,” “The person may become hostile and physically threatening to others” and “physically assaultive,” and “The mood may shift rapidly to anger or depression” (p. 330). The very next page in the *DSM-IV*, repeats the reminder that “Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication. . .” (p. 331).

Mania is characterized by “increased involvement in goal-directed activities” (American Psychiatric Association [2, p. 328]). Therefore, the individual is able to plan and carry out inappropriate or destructive aggressive actions, or to attempt to cover them up once they have been enacted. Individuals undergoing mania often feel uncontrollably driven to carry out elaborate plans, however bizarre, destructive, or doomed they may be.

According to the *DSM-IV*, an “elevated, euphoric or irritable mood” is sufficient to qualify for a diagnosis of Substance-Induced Mood Disorder with *Manic Features* ([2, pp. 370 and 375]; *DSM-IV-TR*, 2000, [3, pp. 405–406]). This descriptor for manic features is sufficiently broad to encompass some or all symptoms associated with stimulation and aggression. Therefore, an SSRI-induced stimulant-like or aggressive reaction can often be diagnosed as an SSRI-Induced Mood Disorder with Manic Features. When drug-induced mood swings occur from mania to depression, sometimes accompanied by switches from violence to suicidality, the diagnosis can include both *depressive* and *manic* features.

Irritability as used in the *DSM-IV* has a more ominous meaning than irritability as it is used in ordinary language. During a discussion of depression, the *DSM-IV* refers to the symptom of “increased irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, or an exaggerated sense of frustration over minor matters)” (p. 321). Many individuals who commit aggression while under the influence of SSRIs will qualify for a Substance-Induced Mood Disorder with Manic Features on the basis of their obvious increase in irritability while taking the drug.

The capacity for SSRIs to induce akathisia – and for akathisia to cause suicidality, aggression, and a worsening mental condition – are also recognized in the *DSM-IV* [2] and the *DSM-IV-TR* [3] in the section dealing with neuroleptic-induced akathisia. *DSM-IV-TR* observes, “Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts.” It also mentions “worsening of psychotic symptoms or behavioral dyscontrol.” It then states, “Serotonin-specific reuptake inhibitor antidepressant medications may produce akathisia that appears identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia” (p. 801).

7.2. *Practice guidelines for major depressive disorder in adults (1993)*

The American Psychiatric Association [1] practice guideline, like the *DSM-IV*, attempts to arrive at a consensus among experts. The emphasis, however, is on treatment rather than diagnosis. Like the *DSM-IV*, the practice guideline was published after the SSRIs were in use.

Using several citations from the literature, the practice guideline states:

All antidepressant treatments, including ECT, may provoke manic or hypomanic episodes. Individuals with a history of mania or hypomania are at particular risk for this untoward effect, although it may occur even in patients with no such history; this complication is estimated to occur in 5–20% of depressed patients treated with antidepressants (p. 22).

Recognition of antidepressant-induced manic-like reactions and akathisia in the most commonly used manual of psychiatric diagnosis has important implications for clinical practice and forensics. Practitioners should be aware that these adverse drug reactions occur and that the patient should be diagnosed with a Substance-Induced Disorder or with akathisia rather than with a primary psychiatric disorder, such as Bipolar I Disorder or an anxiety disorder. It should alert practitioners to the need to stop antidepressants at the first sign of initial or recurring hypomanic and manic symptoms, or akathisia. In forensics, recognition of the existence of these adverse drug reactions can help to establish causality in malpractice, product liability, and criminal cases when SSRIs induce abnormal mental and behavioral reactions. The body of literature reviewed in this report and the confirmation found in the *DSM-IV* and *DSM-IV-TR* help to establish a standard requiring that physicians be aware of the potential for these drugs to cause mania and akathisia with the associated risks of suicidality, violence, and extreme or bizarre behavior.

8. My clinical and forensic experience with similar cases

I have been a medical expert in a number of suits in which children and adults have developed bizarre, irrational, and violent behavior while taking SSRI antidepressants. In one case in California, a man drowned himself and his two small children in a bathtub a few days after starting on paroxetine (see www.breggin.com for this and other legal cases). Also while taking paroxetine, a young adult in South Carolina committed a violent rape and a man in Pennsylvania drove his car into a policeman in order to obtain the officer's gun in order to kill himself. In a fourth case involving paroxetine, in Vermont a 17-year old boy who had missed one or two doses of paroxetine bludgeoned a close friend for no apparent reason. In Florida a teenage girl taking fluoxetine fired a pistol pointblank at another younger but the gun fortunately failed to function. None of these individuals had any history of violence prior to taking SSRIs.

When all of the SSRI antidepressants are included, I have direct clinical and forensic experience with dozens of cases of aggression in association with these drugs.

9. Discussion: “The Drug Made Me Do It”

There is a natural reluctance to attribute “bad behavior” or loss of ethical restraint (dyscontrol, loss of impulse control) to a psychoactive substance. Western philosophy, religion, and tradition tend to hold human beings responsible for their harmful behaviors and eschew “excusing” such behavior on the basis of “mental illness.” Indeed, the concept of mental illness has been subject to challenge by this author and many others. Nonetheless, the weight of considered evidence indicates that psychoactive substances can play a role in causing suicide, violence, and other forms of disinhibited criminal conduct.

First, controlled clinical trials comparing any psychoactive drug to a placebo will typically produce evidence for a pattern of central nervous system adverse drug effects with mental symptoms that are specific for the drug and not for the placebo. For example, SSRI-antidepressants and amphetamine-like agents both tend to produce a continuum of central nervous system stimulation. This physical stimulation will be associated with mental manifestations that range from mild euphoria and irritability to depression and mania, and ultimately to increased rates of both aggression and suicidality.

Second, patterns of reports made to the FDA spontaneous reporting system also make apparent that certain drugs are associated with specific patterns of extreme mental and behavioral reactions (for additional examples and an analysis of methodology, see Breggin [10,11]). Even non-psychiatric medications have been implicated in causing depression and suicidality. Isotretinoin (Accutane), a medication used to treat severe acne, has been found to produce depression and suicidality as demonstrated in numerous clinical reports and in individual case studies. In some clinical cases, “depression subsided with discontinuation of the therapy and recurred with reinstatement of therapy” [65, p. 2872].

Third, many physical disorders also affect mental attitudes and behavior. Hyperthyroidism as well as overdoses of thyroid hormone can increase anxiety, irritability, and other emotions that the individual would not ordinarily experience and that can lead to behavioral abnormalities. There are, of course, many similar examples involving hormones such as testosterone and cortisone. More to the point, accidental brain injury to the frontal lobes and surgical lobotomy usually impair judgment, ethical restraint and self-reflection. The character of the individual is often viewed as “changed” and “worsened.”

Fourth, as an expert in criminal and civil cases, I have studied the lives of many individuals who – under the influence of psychoactive drugs, such as SSRIs, NSRIs, and benzodiazepines – have committed acts of aggression that were wholly alien to their character and antithetical to their prior behavior. It is, of course, well-known that the illegal use of stimulant drugs, such as methamphetamine and cocaine, can be associated with paranoid reactions and violence. As Preda et al. [66] suggest, the SSRIs and hallucinogens such as lysergic acid diethylamide (LSD) may cause psychosis through similar effects on serotonin receptors.

The example of involuntary intoxication under the law helps elucidate the issue of responsibility while under the influence of psychoactive substances. Under the law, an individual is usually held responsible for behavior committed under the influence of alcohol or other non-prescription intoxicants because it is presumed that the individual knew that he was taking a psychoactive substance that can impair judgment and self-restraint. However, in most states an individual can claim *involuntary* intoxication as a mitigating or exonerating factor in a criminal case. For example, if the individual *unknowingly* drank alcohol from “spiked” punch, the involuntary nature of the intoxication might become a mitigating or exonerating factor under the law. Similarly, when an individual takes an antidepressant without knowing that it can cause mania, he or she may be exonerated from the consequences of manic-like behavior.

If an individual involuntarily intoxicates another person, the perpetrator may be guilty of a crime and the victim may be absolved of any contributory responsibility. For example, a man can be judged guilty of rape if he has impaired the consciousness and self-restraint of his victim by surreptitiously slipping a sedative into her water glass. The victim, even if physically conscious during the sexual act, may be exonerated of seeming acquiescence to the assault on the basis of the involuntary intoxication.

The debate over human responsibility will always remain at root ethical and philosophical, as well as a legal. However, empirical data must be taken into account. A mountain of experimental and clinical data, some of it reviewed in this report, supports the concept that psychoactive substances are frequently associated with an increased rate of disturbed mental and behavior reactions, causing some individuals to act as if they have lost their customary ethical restraint and self-control.

It may be argued that some individuals will not lose ethical restraint regardless of the nature or intensity of an involuntary intoxication. However, even if some individuals are immune to behaving badly under the influence of drugs, while others seem especially susceptible, this merely reflects human variation, a factor that complicates most research in medicine and behavioral science. The reality of human variation does not undermine the validity of the association between certain drugs and the relatively frequent production of certain kinds of dangerous mental states and behaviors.

Drug-induced disturbances in mood or in behavior should be viewed as genuine neurological disorders rather than as vague “mental illnesses.” The capacity of speculative “biochemical imbalances” or “genetic factors” to cause or contribute to mania or depression remains unproven. Nor do we know the specific biochemical or neurological mechanisms whereby psychoactive substances cause mental disturbances. But the capacity for psychoactive substances to disrupt brain function and hence mental function is beyond dispute. Furthermore, a great deal of empirical data confirms their capacity to cause disinhibition, mania, depression and other mental phenomena associated with violence toward oneself and others, and other destructive behaviors.

10. Conclusions

There are many reports and studies confirming that SSRI antidepressants can cause violence, suicide, mania and other forms of psychotic and bizarre behavior. Overall, the SSRIs produce violence, suicide and extremes of abnormal behavior by a variety of mechanisms. Teicher et al. [72] suggest nine possible mechanisms: (1) energizing the depressed and suicidal patient, (2) paradoxically worsening the individual’s depression, (3) causing akathisia, (4) causing panic and anxiety, (5) causing manic or mixed manic-depressive states, (6) causing insomnia or disturbances in the sleep architecture, (7) causing obsessive suicidal preoccupations, (8) causing borderline states with hostility, and (9) causing alterations in EEG activity. Teicher et al. document each of these phenomena in their review of the literature and, as this paper indicates, the scientific evidence has grown considerably stronger in the intervening decade.

With the exception of the alteration in EEG activity, my clinical and forensic work has confirmed that each of above SSRI- and NSRI-induced phenomena can cause violent and suicidal behavior. However, my clinical and forensic experiences and reviews of the literature indicate that four syndromes encompass most of the phenomena and describe most of the individual cases:

- (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.

The above syndromes often appear in combination with each other. Often the syndromes will abate within days after stopping the SSRI but sometimes they persist, leading to hospitalization and additional treatment over subsequent weeks or months. Reported rates for these syndromes vary widely but each of them appears to be relatively common. They frequently occur in individuals with no prior history of violence, suicidality, psychomotor agitation, or manic-like symptoms.

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