

SSRIs: Are They As Safe As Promised? Part 2

by Gary Null, PhD and Martin Feldman, MD

In Part 1 of this two-part article, we looked at how Prozac and other selective serotonin reuptake inhibitors (SSRIs) came to lead the market for antidepressants in the 1990s. These drugs have been taken by tens of millions of people, including a growing number of children, even though they have been linked to harmful side effects in some users and certain studies have found that SSRIs do not differ significantly from placebo in treating depression.

In Part 2, we will discuss some of the serious side effects that have been associated with SSRIs, particularly fluoxetine (Prozac). The SSRIs also include paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), and citalopram (Celexa). The adverse effects are:

Akathisia

As noted in Part 1, people may suffer from a variety of side effects when the central nervous system is overstimulated. Studies show that two effects of overstimulation – akathisia and agitation – are experienced by some people who take fluoxetine.

Akathisia can be defined as a need to move about. The person feels anxious or irritable and is compelled to stand up, pace, shuffle his or her feet, and the like. Prozac also can cause extreme agitation, and this condition often is associated with akathisia.

Eli Lilly states in Prozac's information sheet that the drug can cause akathisia. However, the company has said that less than 1% of Prozac users experience this side effect, while a report in the *Journal of Clinical Psychiatry* has estimated that the actual share of Prozac users who suffer from akathisia is 10% to 25%. Typical symptoms included restlessness, constant pacing, purposeless movements of the feet and legs, and marked anxiety.¹ Other reports on the Prozac/akathisia link and SSRI-induced cases of akathisia have appeared in psychiatric and medical journals.²⁻⁹

Bruxism (grinding of the teeth) may be another form of akathisia that occurs in some users of SSRIs. Two researchers discuss four such cases and note that

while definitions of bruxism may be confusing and contradictory, "we believe SSRI-induced bruxism is best conceptualized as a form of akathisia."¹⁰ The literature includes other reports of bruxism that may be associated with SSRI use.¹¹⁻¹³

Akathisia is related to a breakdown in the ability to control impulses. Thus, it has been associated with violent and suicidal acts in a number of studies and reports. One two-year study found a higher akathisia rating among people involved in violent acts than those who observed the incidents.¹⁴ A double-blind clinical study established a link between akathisia and suicidal or homicidal thoughts.¹⁵ Akathisia was associated with acts of extreme violence in an article describing three patients who attacked other people or committed murder.¹⁶

Other researchers have noted that patients who take Prozac and develop akathisia may, in turn, become preoccupied with thoughts of suicide.^{17,18} One article reports on three patients who attempted suicide during fluoxetine treatment and were then reexposed to the drug. The second time around, all three developed severe akathisia and said the condition made them feel suicidal; they also attributed their previous suicide attempts to akathisia.¹⁹ According to one reviewer, studies have suggested that fluoxetine "may in fact lead to suicidal behavior because the drug appears to adversely affect serotonergic neuronal discharge and induce an akathisia-like extrapyramidal reaction."²⁰

Dr. Roger Lane, a scientist at Pfizer (maker of Zoloft), notes in a 1998 article that the occasional occurrence of SSRI-induced extrapyramidal side effects and/or akathisia may be "a consequence of serotonergically-mediated inhibition of the dopaminergic system."²¹ A study of rats concludes that a common characteristic of SSRIs is to inhibit the basal firing rate of dopaminergic neurons in the ventral tegmental area. The drugs' effect on VTA dopaminergic cell activity "might be relevant for their therapeutic action and may explain the origin of the reported cases of akathisia," say the authors.²²

Neurological side effects

A number of movement disorders have been linked to the use of Prozac and other SSRIs since the drugs' introduction. In a 2001 report in *Psychiatric Times*, Raphael J. Leo, MD, says the movement disturbances associated with SSRIs are among the adverse events that were unappreciated in preclinical marketing trials. Although their occurrence may be rare, these side effects are clinically significant and should be of concern to clinicians.²³

In his 1996 review of the literature, Dr. Leo found 71 cases of SSRI-induced extrapyramidal symptoms. The side effects included akathisia (41.5%), dystonia (28.2%), parkinsonism (14.1%), and tardive dyskinesia-like states (11.3%). In addition, there were 16 cases of worsening parkinsonism among patients with existing Parkinson's disease.²⁴ A 1998 review found 127 published reports of SSRI-induced movement disorders, including akathisia, parkinsonism, dystonia, dyskinesia, tardive dyskinesia, mixed disorders, and bruxism. Canadian makers of SSRIs also provided the researchers with reports on parkinsonism (516 reports), dyskinesia (208), tardive dyskinesia (76), bruxism (60), akathisia (49), and dystonia (44).²⁵ A 2001 review found about a hundred detailed reports linking SSRIs to acute dystonia, akathisia, the onset or aggravation of parkinsonism, and in rare cases, late-onset dyskinesias.²⁶ And a 1999 analysis of 1,861 adverse reactions submitted to a Swedish committee found that neurological symptoms were the most commonly reported reactions.²⁷

The literature links fluoxetine to a variety of specific neurological symptoms, including acute dystonia and reversible dystonia,²⁸⁻³⁰ acute paroxysmal dystonia, which the researchers believe to be the first reported case induced by fluoxetine,³¹ complex movement disorders,³² tardive dyskinesia and dyskinesia (some patients were also taking other drugs),³³⁻³⁶ and torticollis, bradykinesia, and cogwheel rigidity in a 15-year-old.³⁷

Tardive dystonia and tardive dyskinesia are two forms of neurological

damage in which the muscles tense up or move involuntarily. These disorders can produce bizarre-looking postures and movements. Consequently, people who are taking Prozac to relieve mental illness may in fact appear to be mentally ill. The symptoms may continue after the drug is stopped, and in some cases the condition may be permanent. One article notes that in most cases, tardive dyskinesia-like symptoms did not improve when Prozac was discontinued.³⁸

The risk of adverse neurological effects from SSRIs also extends to newborns whose mothers took the drugs during late pregnancy, according to a 2003 article. This prospective, controlled study found a significant, fourfold difference in serotonin-related symptoms during the first four days of life between infants exposed to SSRIs and a control group. The most common symptoms included tremor, restlessness, and rigidity. By two weeks of age, no significant difference in symptoms was detectable between the two groups.^{39,40} Other articles suggest that prenatal exposure to SSRIs may have subtle effects on infants' motor development and motor control⁴¹ and that prolonged exposure alters the neonatal acute pain response.⁴²

In *Prozac Backlash*, Joseph Glenmullen, MD, presents the view that all of the neurological side effects of SSRIs originate in the brain's involuntary motor system. While the exact mode of action is not known, the leading hypothesis is that an unnatural boosting of serotonin affects the levels of dopamine. It is dopamine that has been implicated in these neurological disorders, Dr. Glenmullen says, and research shows "a strong link between serotonin and dopamine in the involuntary motor system."⁴³ He quotes one researcher who states that "serotonin seems to modulate dopamine function"⁴⁴ and points to evidence that the elevation of serotonin causes a compensatory drop in dopamine. In three studies, reductions in dopamine were caused by Prozac (57% drop), Celexa (50% drop), and Zoloft.⁴⁵⁻⁴⁷ The latter researchers say that "motor activity is highly dependent on a balanced dopaminergic system."⁴⁸

Dr. Glenmullen concludes that "the Prozac group's much-touted 'selectivity' may, in fact, be a liability: Boosted beyond ordinary levels, elevated serotonin could trigger a dangerous backlash, a compensatory drop in

dopamine, resulting in the drugs' most severe neurological side effects."⁴⁹ Prozac is not "selective" if it has indirect effects on other neurotransmitters. He cites research showing that SSRIs affect neurotransmitters besides serotonin and dopamine.⁵⁰⁻⁵³

Psychosis

A person's nervousness may reach a psychotic level when the over-stimulation of the nervous system is severe. People can become paranoid,

extremely depressed, suicidal, and dangerous to others. The mental effects of fluoxetine treatment have been discussed in several reports.⁵⁴⁻⁵⁶ In one study of SSRIs and newer atypical agents, 8.1% of all admissions to the psychiatric unit of a general hospital during a 14-month period were due to antidepressant-associated mania or psychosis.⁵⁷

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SSRIs

The ability of Prozac-type drugs to induce mania or hypomania in patients has been documented in a number of medical journals.⁵⁸⁻⁷³ Studies also show that Prozac can produce mania or manic-like symptoms in children and adolescents.^{74,75} A clinical trial of 40 youths (ages 11-17) with obsessive-compulsive disorder found that 30% of those treated with SSRIs developed manic or hypomanic symptoms. Patients taking fluoxetine experienced mania at doses as low as 10 mg a day.⁷⁶ Another report discusses five depressed adolescents (ages 14-16) who experienced mania while taking fluoxetine.⁷⁷

One study suggests that the mania associated with antidepressants may be a distinct clinical entity from spontaneous mania, with episodes that are milder and more time-limited. In this blind, retrospective chart review, patients with drug-associated manic states had significantly less severe levels of delusions, hallucinations, psychomotor agitation, and bizarre behavior than did those with spontaneous mania. The results also showed that MAOIs and the antidepressant bupropion (Wellbutrin) may be associated with milder manic states than are fluoxetine or tricyclic drugs.⁷⁸

Suicide

Beyond the link between akathisia and acts of violence, some users of Prozac have said that the drug caused them to develop suicidal thoughts and obsessions. This aspect of the drug has generated controversy and led to discussions in both medical publications and the general media about the connection between Prozac and other SSRIs and suicide and acts of violence.⁷⁹⁻¹⁰¹

It should be noted that in several studies, the findings suggest that Prozac and/or other SSRIs did not lead to suicidal preoccupation or found that the drugs were not associated with an increased risk of suicidal acts. The safety of the drug also is supported by literature reviews, reports on clinical experiences with Prozac and its effects following an overdose, and reports on clinical trial results or analyses of pooled data from clinical trials.¹⁰²⁻¹¹⁹

The association between fluoxetine and suicide is not easy to dismiss, however. As Richard DeGrandpre reports in "The Lilly Suicides," the FDA had received 2,000 reports of suicides by Prozac users by the spring of 1999, and the FDA itself has estimated that only about 1% of serious side effects are reported to its adverse event system.¹²⁰ Dr. David Healy, director of the North Wales Department of Psychological Medicine at the University of Wales, has used figures from Eli Lilly and independent research to estimate that "probably 50,000 people have committed suicide on Prozac since its launch, over and above the number who would have done so if left untreated," according to a report in the *Boston Globe*.¹²¹ This estimate would be much larger for all SSRIs.¹²²

The controversy over the SSRI/suicide connection flared up again in June 2003 when the Food and Drug Administration recommended that Paxil no longer be prescribed to children and adolescents under the age of 18 to treat depression. The agency was reviewing reports of a possible increased risk of suicidal thinking and

suicide attempts in young people who took the drug for major depressive disorder. The research under review also showed that Paxil is no more effective than placebo in treating these patients' depression.^{123,124} The FDA's warning closely followed a statement by the UK's Committee on Safety of Medicines that Seroxat (paroxetine's brand name there) should not be used for depression in the under-18 population for the same reasons.^{125,126}

In late October 2003, the FDA then issued a Public Health Advisory to health-care professionals regarding reports of suicidality in clinical trials for various antidepressants in young people with major depressive disorder. Preliminary data for eight drugs (five SSRIs plus mirtazapine, nefazodone, and venlafaxine) suggested an excess of suicidality reports (suicidal ideation and suicide attempts) for patients assigned to several of the antidepressants compared to those taking placebo. While there were no reports of completed suicides in the 20 placebo-controlled trials the FDA was considering for the eight drugs, the agency said it had not, at that point,

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"been able to rule out an increased risk of suicidality for any of these drugs." The FDA said that additional data and analysis were needed, along with a public discussion of the available data, and scheduled a meeting before two advisory committees on February 2, 2004.¹²⁷

What follows is some of the research on the association between Prozac and other SSRIs and self-destructive thoughts and behavior:

- In the Paxil matter discussed above, the results of three (unpublished) placebo-controlled clinical trials showed that the risk of suicidal thinking and suicide attempts was about three times greater with the under-18 Paxil users than in the placebo group.^{128,129} When releasing this information, the FDA said "there is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults."¹³⁰

- A 2003 review by Dr. Healy of randomized controlled trials, meta-analyses of clinical trials, and epidemiological studies on the SSRI/suicidality issue concluded that "the

data reviewed here make it difficult to sustain a null hypothesis that SSRIs do not cause problems in some individuals."¹³¹

- In a large-scale analysis of clinical trial data for psychotropic drugs approved by the FDA between 1985 and 2000, Dr. Arif Khan found that patients attempted and completed suicide substantially more often than expected. The analysis included more than 71,604 patients treated with atypical antipsychotics, SSRIs, and other drugs, according to an article in *Clinical Psychiatry News* on Dr. Khan's presentation at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.¹³²

The findings: Compared with a suicide rate of 11/100,000 people per year in the general population, the suicide rates per 100,000 were 752 in antipsychotic trials, 718 in antidepressant trials, 425 in trials for social anxiety disorder, 136 in panic disorder, and 105 in obsessive-compulsive disorder. Dr. Khan found this data particularly surprising

because most clinical trials try to exclude patients who are actively suicidal.¹³³

- A 1990 study reported on the "surprising possibility that fluoxetine [Prozac] may induce suicidal ideation in some patients." The study, conducted by Dr. Martin Teicher and colleagues at Harvard Medical School, concerned six patients who were depressed but not suicidal before they started taking Prozac. Within weeks of taking the drug, said the researchers, the patients experienced "intense, violent suicidal preoccupation."¹³⁴

- In an analysis of 1,017 patients treated with antidepressant drugs by 27 psychiatrists, researchers found that 3.5% of those who took fluoxetine alone and 6.5% of those who took fluoxetine and tricyclics became suicidal only after their treatments began. The researchers concluded that the incidence of suicidal ideation was not significantly different between patients taking Prozac alone and those taking other drugs.¹³⁵ According to Dr. Glenmullen, however, when Dr. Teicher of Harvard Medical School re-evaluated the data of Fava and Rosenbaum, he found that Prozac patients were at least threefold more likely to develop new suicidal ideation than those taking older antidepressants. Other experts have agreed with Dr. Teicher's reanalysis.¹³⁶

- A Prozac study involving children aged 10 to 17, conducted at the Yale University School of Medicine, found that "suicidal ideation of self-injurious behavior persisted for up to one month after the fluoxetine was discontinued."¹³⁷

- Psychiatrist William Wirshing and associates reported on five patients who developed akathisia when they took Prozac. They noted that the condition may have accounted for suicidal ideation in the patients.¹³⁸

High-profile lawsuits against Eli Lilly and other SSRI manufacturers also illuminate the effects of these drugs on some users.¹³⁹⁻¹⁴¹ Perhaps the most notorious of these cases concerns Joseph Wesbecker, who in 1989 shot 20 people, eight of them fatally, and killed himself while taking Prozac.¹⁴² This case, the first of the Prozac lawsuits to go to trial, was reported as a victory for

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SSRIs

➤ Eli Lilly, but it has been learned that the company secretly settled the case during the trial, according to DeGrandpre. The only other such Prozac case to go to trial was that of William Forsyth, a 61-year-old man who killed his wife and himself 11 days after he began taking Prozac. A jury found in favor of Eli Lilly in 1999. Of the 160-plus similar cases brought

against Eli Lilly by 1994, many have been dismissed and others have been settled.¹⁴³

In defense of Prozac, Eli Lilly says that the drug's safety has been thoroughly documented and that scientific evidence shows Prozac and other antidepressants appear to protect against violent and suicidal behavior. The company also points to the findings of a 1991 panel convened by the FDA.¹⁴⁴ The panel voted 10 to 0 that there was no evidence proving antidepressants were linked to violent or suicidal thoughts and behaviors.

But according to the *New York Times*, experts hired by lawyers suing SSRI manufacturers over the suicide issue "question whether the FDA received a full picture of the available research in 1991," such as the initial refusal by German regulators in 1985 to approve Prozac for sale because of concerns about suicide (the drug was approved there after all). And now, seven of 10 members of the FDA's 1991 panel say the recent information about a suicide risk in young users of Paxil "would prompt them to reconsider that decision, if they were asked."¹⁴⁵

Depression

People who are overstimulated may end up suffering from depression as well. Eli Lilly knew that Prozac caused depression and reported the relationship to the FDA, according to Peter R. Breggin, MD, author of *Talking Back to Prozac*. "Lilly admitted on paper, in its final statement about the drug's side effects, that it commonly caused patients to get depressed. Then it got scratched out at the FDA... It just disappeared from the label."¹⁴⁶

The result is that a drug intended to relieve depression may have the opposite effect. As Dr. Breggin states, "[People] start taking the drug and in the beginning they feel better.... Maybe the drug gives them a burst of energy. Stimulants will do that. They make people feel energized. Then they get more depressed. They may get suicidal feelings. They don't know that Eli Lilly once listed depression as an effect of the drug. And so they end up thinking they need more Prozac, and their doctor agrees."¹⁴⁷

In a related area, doctors at Johns Hopkins University School of Medicine reported that five patients developed apathy, indifference, and loss of initiative when they took fluoxetine or

fluvoxamine. The doctors noted that the mechanisms producing these side effects bore a clinical resemblance to "those of frontal lobe dysfunction," in which patients may "display apathy, flatness of affect and lack of emotional concern, childishness and euphoria, socially inappropriate behavior, and difficulty in foreseeing the outcome of an action."¹⁴⁸ Another report on an obsessive-compulsive patient who developed apathy, indifference, inattention, and perseveration when taking high doses of fluoxetine states that the effects were associated with "changes in neuropsychological tests generally associated with frontal lobe impairment."¹⁴⁹

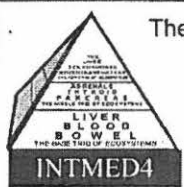
A recent article was the first to report on a "frontal lobe syndrome" in children and adolescents who took SSRIs. The authors present five cases of apathy and lack of motivation in a child and four adolescents. The symptoms were related to dosage and reversible. The authors concluded: "The subtlety of symptoms, lack of insight in patients, disabling effects, and delayed onset indicate a need for clinicians to inform families of these potential symptoms when SSRIs are prescribed."¹⁵⁰

Researchers suggest in a 2002 article that "emotional blunting" may be an underappreciated side effect of SSRIs.¹⁵¹ In their research, 15 patients reporting SSRI-induced sexual dysfunction completed a questionnaire about their emotions (the outcome measure admittedly lacked evidence of validity¹⁵²). Compared to controls, the SSRI users reported significantly less ability to cry, irritation, care about others' feelings, sadness, erotic dreaming, creativity, surprise, anger, expression of their feelings, worry over things or situations, sexual pleasure, and interest in sex.¹⁵³

Sexual dysfunction

Indeed, Prozac's effects on serotonin also can induce sexual dysfunction. Sexual side effects are common in people taking antidepressant drugs, according to research, but the effects often are underreported by patients and underestimated by physicians. Adverse effects include orgasm dysfunction, delayed ejaculation, erectile difficulties, and reduced desire.

Eli Lilly acknowledges that the incidence of "untoward sexual experience and performance" is likely



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to be underestimated in product labeling, partly because patients and doctors may be reluctant to discuss this topic. The company's placebo-controlled clinical trials for major depressive disorder, OCD, and bulimia in the US found that decreased libido was the only sexual side effect reported by at least 2% of people taking fluoxetine (in combined data for a pool of studies, 4% of patients on the drug reported this effect versus <1% on placebo).¹⁵⁴

The medical literature reports higher rates. A cross-sectional study of 6,297 outpatients in 1,101 US primary care clinics found sexual dysfunction rates of 36% to 43% for SSRIs and two other antidepressants.¹⁵⁵ In a study of 1,022 outpatients, the incidence of sexual dysfunction with SSRIs ranged from 57.7% for fluoxetine to 72.7% for citalopram (Celexa).¹⁵⁶ A study of 107 outpatients concluded that three SSRIs – fluoxetine, paroxetine (Paxil), and sertraline (Zoloft) – “to an equal degree significantly decreased libido, arousal, duration of orgasm, and intensity of orgasm below levels experienced pre-morbidly.” Only 27% of patients on SSRIs had no adverse sexual side effects.¹⁵⁷ In a study of 235 outpatients, 62.6% reported one or more sexual dysfunctions when taking serotonin reuptake inhibitors. The rates included 28.9% for citalopram, 39% for fluoxetine, 75.5% for paroxetine, and 78.8% for sertraline.¹⁵⁸

Other studies and reviews confirm a high incidence of sexual dysfunction in people taking SSRIs.¹⁵⁹⁻¹⁶² A review of the literature from 1986 to 2000 states that SSRIs “appear to be the class of antidepressants most likely to cause sexual dysfunction.”¹⁶³ However, another review concludes that the literature “is not sufficiently robust to support claims for differences in the incidence of drug-induced sexual dysfunctions between existing antidepressant therapies.”¹⁶⁴ The authors of one study note that sexual side effects may be “substantially underreported unless patients are specifically asked about” them.¹⁶⁵ Another study found that the incidence of sexual dysfunctions increased from 14% when patients reported spontaneously to 58% when physicians asked direct questions.¹⁶⁶

In terms of specific sexual side effects, a number of articles report on the association between SSRIs and orgasm dysfunction, such as delayed

orgasm, anorgasmia, or lower orgasm quality.¹⁶⁷⁻¹⁷² Other reports document cases of prolonged erection and loss of ejaculation or sexual stimulation as a side effect of Prozac.^{173,174} Patients also report drug-related impairment of sexual drive/desire.¹⁷⁵

Cases of sexual dysfunction may subside when the drug is discontinued.¹⁷⁶ In one study, patients experienced substantial improvement in sexual function when the SSRI was reduced in dosage or withdrawn.¹⁷⁷ Possible solutions to drug-induced sexual side effects include waiting for tolerance to develop, reducing the drug dosage, switching to another antidepressant, or adding on another drug to manage the sexual symptoms.¹⁷⁸⁻¹⁸¹ Another management strategy is a “drug holiday,” in which the patient stops taking the medicine for several days (such as the weekend). In a study of SSRI drug holidays among 30 patients, those taking sertraline and paroxetine reported significant improvement in sexual functioning while those taking fluoxetine did not.¹⁸²

Withdrawal side effects

A variety of withdrawal symptoms have been associated with SSRIs (the incidence varies with the half-life of the particular drugs). These symptoms include problems with balance, gastrointestinal and flu-like symptoms, sensory disturbances (such as tingling and electric shock sensations), sleep disturbances (insomnia and vivid dreams), anxiety and/or agitation, crying spells, and irritability.^{183,184}

A number of class action and individual lawsuits have been filed against GlaxoSmithKline by users of Paxil suffering from withdrawal reactions.^{185,186} Some evidence shows the manufacturer knew early on that Paxil could cause withdrawal symptoms. According to a report in *The Guardian*, Dr. David Healy, who testified in a wrongful death lawsuit against GlaxoSmithKline and had access to certain archives, found research from the 1980s showing that healthy volunteers had withdrawal

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symptoms when they went off the drug. On average, about half the volunteers in a group of studies had symptoms.¹⁸⁷ The FDA required that GlaxoSmith-Kline provide stronger warnings about Paxil withdrawal in the drug's label in December 2001.¹⁸⁸

The authors of one report say that health-care professionals need to be aware of the potential adverse effects of stopping an SSRI since they may be mistaken for an illness or a recurrence of depression. A misdiagnosis may result in unnecessary and costly care.¹⁸⁹

Conclusion

Prozac and other SSRIs have been associated with a number of serious side effects since the drugs were brought to market. Yet some researchers have found that an SSRI did not differ significantly from placebo in studies of depression. As a result, health-care professionals need to consider their options carefully in treating patients.

Dr. Irving Kirsch, whose analysis of FDA data found only a small difference in the response to placebos and to SSRIs,¹⁹⁰ suggests there are many interventions – such as physical exercise, psychotherapy, and bibliotherapy (the use of reading materials in psychiatric therapy) – that seem to be “as effective or nearly as effective as antidepressants.” Long-term comparative studies show that psychotherapy is superior to medications. Dr. Kirsch concludes, “Given these data, antidepressant medication might best be considered a last resort, restricted to patients who refuse or fail to respond to other treatments.”¹⁹¹

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