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SSRI DISCONTINUATION SYNDROME – A REVIEW

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ABSTRACT

SSRI discontinuation syndrome, in light of the multitude of prescribed agents, has been disputed. SSRI discontinuation syndrome result from a global downregulation of serotonin receptors in response to increased levels of serotonin in the synaptic cleft, but the specific mechanism through which this creates symptoms is not understood. This review discussed on clinically significant indications of difficulties with the discontinuing of SSRIs, history, mechanism of action, prevention and treatment.

Keywords: SSRI discontinuation syndrome, Prevention, Treatment.

INTRODUCTION

SSRI discontinuation syndrome, also known as SSRI cessation syndrome, is a syndrome that can occur following the interruption, dose reduction, or discontinuation of SSRI (selective serotonin re-uptake inhibitor) or SNRI antidepressant medications. The condition often begins between the time of reduction in dosage or complete discontinuation, depending on the elimination half-life of the drug and the patient's metabolism.

The particulars of the syndrome, in light of the multitude of prescribed agents, have been disputed. Nonetheless, double-blind placebo controlled trials demonstrate statistically and clinically significant indications of difficulties with the discontinuing of SSRIs [1].

Signs and symptoms

The indicators of SSRI discontinuation syndrome are the following:

- Interruption, cessation, or reduction of dosage in an SSRI treatment that has lasted four or more weeks.
- Symptoms which:
- Interfere with normal social, occupational, or other functioning.
- Are not due to another medical condition, drug use, or discontinuation.
- Are not due to a relapse of the condition for which the SSRI was originally prescribed.

Neurological

Symptoms described as brain zaps, brain shocks, brain shivers, brain pulse-waves, head shocks, pulses, flickers, or cranial zings are withdrawal symptoms experienced during discontinuation (or reduction of dose) of antidepressant drugs. These result from a global downregulation of serotonin receptors in response to increased levels of serotonin in the synaptic cleft, but the specific mechanism through which this creates symptoms is not understood. Common responses to dose reduction or cessation include dizziness, electric shock-likesensations, sweating, nausea, insomnia,tremor, confusi on, nightmares, and vertigo. The MedDRA preferred term for coding these types of symptoms in adverse drug reaction reports is paraesthesia [2].

In a 1997 survey in north-east England, a sizable minority of medical professionals were not confidently aware of the existence of antidepressant withdrawal symptoms. A 2005 review of adverse event reporting

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showed that descriptions of electric shocks from patients on paroxetine had been reported more frequently than some other symptoms.

History

The first report of withdrawal symptoms occurring after SSRI discontinuation was for fluvoxamine (brand names Luvox (US), Faverin (UK)) in 1992. The Committee on Safety of Medicines in the United Kingdom reported withdrawal symptoms involving paroxetine (Paxil, Seroxat) in 1993, and the American Journal of Psychiatry revealed the same for sertraline (Zoloft, Lustral) the following year.

In 1996, Eli Lilly and Company sponsored a symposium to address the increasing number of reports of patients who had difficult symptoms after going off their antidepressants:

By then it had become clear that drug-company estimates that at most a few percent of those who took antidepressants would have a hard time getting off were far too low. Jerrold Rosenbaum and Maurizio Fava, researchers at Massachusetts General Hospital, found that among people getting off antidepressants, anywhere from 20 percent to 80 percent (depending on the drug) suffered what was being called antidepressant withdrawal [3].

The World Health Organization (WHO) continues to track withdrawal syndrome, and notes:

SSRIs are an example of how a conceptual confusion over terminology can affect proper reporting, interpretation and communication of adverse drug reactions related to dependence. To avoid the association with dependence, an increasing number of researchers have used a different term, discontinuation syndrome, instead of withdrawal syndrome. The number of hits for discontinuation syndrome in searches of the international medical literature began to increase, relative to the occurrence of withdrawal syndrome, in 1997 after [the Eli Lilly] symposium on antidepressant discontinuation syndrome held in 1996. In fact, dependence syndrome has been reported to the Uppsala Monitoring Centre for all SSRIs through the same postmarketing surveillance systems, although there are significantly fewer reports of dependence syndrome than of withdrawal syndrome.

The same WHO note ranks antidepressants according to withdrawal, with paroxetine having the highest number of withdrawal syndrome reports and fluoxetine the highest number of drug dependence reports; the note concludes, Three SSRIs are among the 30 highest-ranking drugs in the list of drugs for which drug dependence has ever been reported to the Uppsala Monitoring Centre database; a total of 269 reports had been received as of June 2002 (109 reports for fluoxetine, 91 for paroxetine and 69 for sertraline) [4].

Cause

The cause is the abrupt cessation, or rapid tapering of one of the SSRIs or SNRIs.

- citalopram (Celexa, Cipramil, Celepram, Emocal, Sepram, Seropram)
- escitalopram (Lexapro, Cipralex, Esertia, Esipram)
- fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin [EUR])
- paroxetine (Paxil, Seroxat, Pexeva, Aropax, Deroxat, Paroxat)
- sertraline (Zoloft, Lustral, Serlain)
- dapoxetine (Priligy)
- fluvoxamine (Luvox, Fevarin, Favoxil)
- venlafaxine (Effexor, Efexor)
- desvenlafaxine (Pristiq)
- duloxetine (Cymbalta)
- vilazodone (Viibryd) [5]

Post-SSRI sexual dysfunction

According to one source, post-SSRI sexual dysfunction (PSSD) is an iatrogenic type of sexual dysfunction caused directly by the previous use of SSRI antidepressants.

Diagnosis

Although most SSRIs are widely used and generally considered safe, an abrupt cessation, or rapid tapering of SSRI use may result in a discontinuation syndrome that can mimic serious illness and can be very distressing and intensely uncomfortable. Several pharmacokinetic and pharmacodynamic factors influence the frequency and onset of these symptoms. When allowed to run its course, the syndrome duration is variable (usually one to several weeks) and ranges from mild-moderate intensity in most patients, to extremely distressing in a smaller number of patients who may have side effects for months.

With the lack of a definition based on consensus criteria for the syndrome, a discontinuation panel met in Phoenix, Arizona in 1997 and stated: SSRI discontinuation symptoms... may emerge when an SSRI is abruptly discontinued, when doses are missed, and less frequently, during dosage reduction. In addition, the symptoms are not attributable to any other cause and can be reversed when the original agent is reinstituted, or one that is pharmacologically similar is substituted. SSRI discontinuation symptoms, in most cases, may be minimized by slowly tapering antidepressant therapy, but there have been several case reports where symptoms occurred consistently even through repeated attempts to taper therapy. Physical symptoms include problems with balance, gastrointestinal and flu-like symptoms, and sensory and sleep disturbances. Psychological symptoms include anxiety and/or agitation, crying spells, irritability and aggressiveness [6].

A 2000 study at the Department of Psychiatry at Dalhousie University in Halifax, Nova

Scotia constructed diagnostic criteria for SSRI discontinuation syndrome. These criteria are 2 or more of the following symptoms developing within 1 to 7 days of discontinuation or reduction in dosage of an SSRI after at least 1 month's use, when these symptoms cause clinically significant distress or impairment and are not due to a general medical condition or recurrence of a mental disorder: dizziness, light-headedness, vertigo or feeling faint; shock-like sensations or paresthesia; anxiety; diarrhea; fatigue; gait instability; headache; insomnia; irritability; nausea or emesis; tremor; and visual disturbances.

Due to the lack of peer reviewed diagnostic criteria, many physicians, unaware of the potential severity of discontinuation syndrome, do not get informed consent at the time of initial prescription from the patient (though patients in clinical trials do), so this syndrome can be an unexpected barrier to patients attempting to discontinue the drug. In addition, warnings to patients not to stop taking the drug without doctor's approval, while indicated, may lead to a reluctance to discontinue SSRI therapy in patients who need not take the drugs long-term [7].

Definition of withdrawal

As described in the History section above, SSRI withdrawal syndrome began to be called SSRI Discontinuation syndrome following a symposium in 1996; since then, the terms have been used interchangeably. SSRIs are not addictive in the conventional medical use of the word (i.e. animals given free access to the drug do not actively seek it out and do not seek to increase the dose), but discontinuing their use can produce both somatic and psychological symptoms thereby providing negative feedback to continue taking the drug.

Critics argue that the pharmaceutical industry has a vested interest in creating a distinction between addiction to recreational or illegal drugs and dependence on antidepressants. Arguments against the use of the term withdrawal are primarily predicated on not frightening patients or alienating potential customers who may or may not need the medication.[17] According to the consensus definition by the American Academy of Pain Medicine, withdrawal is a symptom of Physical Dependence, not of Addiction and as such the word withdrawal is appropriate to the symptoms caused by ceasing an SSRI [8].

Mechanism

The exact mechanism of SSRI withdrawal syndrome is unknown, and may be due to a variety of factors. Continuing research on discontinuation/withdrawal syndrome has attributed SSRI withdrawal syndrome to electrophysiological changes in the brain (particularly on the 5-HT receptor), and electrophysiological changes in the body (nerve growth factor) in the absence of the SSRI, as well as dopamine dependency, and an over-excited immune system.

The central nervous system (CNS) adapts to the presence of psychoactive drugs. Such adaptation commonly involves the readjustment of neuroreceptors to compensate for the acute pharmacological action of the medication. Desired drug effects may be mediated by such compensatory changes which may explain the delayed onset of therapeutic effect of antidepressants. This adaptation theory also explains why withdrawal symptoms and signs can occur on the discontinuation of such medications as clearance of drug can occur at a rate faster than the brain can readjust to the absence of medication. Hence, pharmacodynamic and pharmacokinetic factors contribute to the risk of a withdrawal syndrome. Pharmacodynamic factors explain why withdrawal syndromes are often a class issue and why the administration of a drug in the same class often relieves withdrawal symptoms. Formal studies have not characterized the relative risk [9].

One theory states that SSRI withdrawal syndrome is associated with a rostral anterior cingulate Cho/Cre metabolite ratio decrease that may reflect dynamics of rostral anterior cingulate cortex (ACC) function. The ACC appears to play a role in a wide variety of autonomic functions, such as regulating heart rate and blood pressure, and is vital to cognitive functions, such as reward anticipation, decision-making, empathy, and emotion. Neuroscientists indicate the dorsal anterior cingulate cortex is primarily related to rational cognition while the ventral is more related to emotional cognition [10].

A separate study demonstrated that changes in regional central blood volume of left prefrontal cortex and left caudate nucleus correlate with the emergence of withdrawal symptoms and increased Hamilton Depression Rating Scale after interruption of paroxetine treatment. The findings supported the hypothesis that brain regions implicated in depression, with extensive serotonergic innervation, would exhibit changes in activity associated with emergence of symptoms following drug discontinuation. Cerebral blood volume maps were obtained via dynamic susceptibility functional magnetic resonance imaging (fMRI).

There is speculation concerning the possibility of a temporary deficiency of synaptic serotonin with abrupt withdrawal of an SSRI. This deficiency is compounded by the fact that down-regulated receptors will remain in their relatively hypoactive state for days to weeks. This is believed to result in antidepressant discontinuation syndrome directly or indirectly via downstream effects on other neurotransmitter systems (e.g., norepinephrine, dopamine, and GABA) implicated in depressive and anxiety disorders [11]. Another possible mechanism is by

inhibition of dopaminergic neurotransmission.

Persistent adverse effects

In a very few cases, discontinuation of SSRIs may result in sexual dysfunction (loss of libido, genital anesthesia, erectile dysfunction) that persists for years or forever after the fact. Long term withdrawal syndromes outside of sexual dysfunction from SSRIs are not well documented. One Italian study found that in patients with panic disorder and agoraphobia, 45% exhibited a discontinuation syndrome that disappeared within a month in all but 11%. Symptoms of the discontinuation syndrome include agitation, anxiety, akathisia, panic attacks, irritability, hostility, aggressiveness, worsening of mood, dysphoria, crying spells or mood lability, overactivity or hyperactivity, depersonalization, decreased concentration, slowed thinking, confusion, and memory/concentration difficulties [15].

Most cases of discontinuation syndrome last between one and four weeks but a substantial minority, perhaps up to 15% of users, have persistent withdrawal symptoms evident one year post-withdrawal. Paroxetine and venlafaxine seem to be particular difficult to discontinue and prolonged withdrawal syndrome lasting over 18 months have been reported with paroxetine.[34]

Discontinuation of SNRIs

SNRIs affect both reuptake inhibition of serotonin and norepinephrine. The two mostly widely prescribed SNRIs are venlafaxine and duloxetine. To these has been added desvenlafaxine. In addition, the widely used analgesic Tramadol, which is molecularly similar to venlafaxine, has been cited as it has SNRI properties which typically are known to affect patients after 3 months or more use in therapeutic doses of 400 mg per day.

Venlafaxine

Sudden discontinuation of venlafaxine (brand name Effexor) has a high risk of causing potentially severe withdrawal symptoms. Even missing a single dose can cause symptoms of withdrawal. The high risk of withdrawal symptoms reflects venlafaxine's short half-life as well as its effect as a dual uptake inhibitor. Discontinuations have a tendency to be significantly stronger than the withdrawal effects of other antidepressants including the tricyclic antidepressants, but are similar in nature to those of SSRIs with a short half-life such as paroxetine [16].

Symptoms of discontinuation are similar to other antidepressants including irritability, restlessness, headache, nausea, fatigue, excessive sweating, dysphoria, tremor, vertigo, irregularities in blood pressure, dizziness, visual and auditory hallucinations, feelings of abdominal distension, and paresthesia. Other non-specific mental symptoms may include impaired concentration, bizarre dreams, delirium, cataplexy, agitation, hostility, and worsening of depressive symptoms. Online help groups consistently mention withdrawal from venlafaxine as triggering dreams of a particularly distressing and hellish quality. Electric shock sensations have also been reported with many patients describing the symptoms as brain zaps. It has been suggested the sensations may represent an alteration of neuronal activity in the central nervous system.

Studies by Wyeth-Ayerst, the maker of venlafaxine, and others have reported severe withdrawal cases, including withdrawal as the presentation of a stroke, as well as neonatal withdrawal (neonatal withdrawal has also been reported with paroxetine, fluoxetine, sertraline, and citalopram). In some venlafaxine withdrawal cases, successful discontinuation was eventually achieved by the addition of fluoxetine, which was later discontinued itself without difficulty. Additionally, use of tramadol has been proven effective as anti-depressant withdrawal aid especially with venlafaxine [14-16].

Duloxetine

Eli Lilly and Company, the manufacturer of duloxetine (brand name Cymbalta) warns that one should not suddenly stop taking this medicine, as this may cause withdrawal symptoms such as dizziness, pins and needles sensations, nausea, difficulty sleeping, intense dreams, headache, tremor, agitation or anxiety. Withdrawal symptoms are temporary and are not the same as addiction. These responses could constitute physical dependence on the drug, but SSRI users do not experience the craving, impulsive use, or long-term relapse risk seen in drug addiction.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, aggressiveness, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Many patients on the drug longer than the Lilly test trials on discontinuation (which only studied patients after 9 weeks of exposure to Cymbalta), report anecdotal

evidence of major withdrawals from Cymbalta lasting from weeks to many months. Since duloxetine is a newer drug (FDA-approval 2004), not many peer-reviewed articles have been published on its adverse effects or withdrawal phenomena, and effects of long term use are still unknown [17].

Fluoxetine as an intervention

Many doctors advise patients who are suffering from SSRI discontinuation syndrome to use fluoxetine as a substitute for their current drug.[37] Substituting fluoxetine in the final stages of SSRI discontinuation, or post discontinuation, provides a rate of reduction of antidepressant which can minimize or eradicate withdrawal symptoms in the patient. Fluoxetine migrates slowly from the brain to the blood. The active metabolite of fluoxetine remains a long time in the brain because it is lipophilic, with a biological half-life of 4 to 8 days (the longest of any SSRI). Therefore the level of the drug in the body falls slowly at a rate to which the brain can adjust when the dosage is reduced. Fluoxetine is also available in a liquid formula, allowing the physician to titrate the drug with greater ease (e.g., with an oral syringe).

In a randomized trial, abrupt interruption of antidepressant therapy for 5–8 days was associated with the emergence of new somatic and psychological symptoms with the highest degree in patients treated with paroxetine and to a lesser degree sertraline, with few symptoms seen with fluoxetine.

- Fluoxetine for clomipramine withdrawal symptoms was reported in 1999 by F. Benazzi.
- Fluoxetine was indicated to cover serotonergic discontinuation syndromes for cessation of paroxetine associated with withdrawal or discontinuation symptoms.

Neonatal withdrawal

The U.S. Food and Drug Administration (FDA) issued a warning on July 19, 2006 that nursing mothers on SSRIs must discuss treatment with their physicians.

When taken by pregnant women, selective serotonin reuptake inhibitors (SSRIs) cross the placenta and have the potential to affect newborns. Although SSRIs have not been associated with congenital malformations, some evidence suggests that they are associated with neonatal complications such as neonatal abstinence syndrome (NAS) and persistent pulmonary hypertension (PPH).

SSRI withdrawal syndromes have been documented in neonates. Investigators found that by November 2003, a total of 93 cases of SSRI use associated with either neonatal convulsions or withdrawal syndrome had been reported. Subsequently, the authors of a study published in The Lancet concluded that doctors should avoid or cautiously manage the prescribing of these drugs to pregnant women with psychiatric disorders.

Prevention and treatment

Patients should be advised of the elimination half-life times of their specific medication, and patients should be aware if changing from a long half-life medication such as fluoxetine (Prozac), to a shorter one, that taking their dose regularly becomes much more important. Patients taking fluoxetine can often miss several doses without noticing any discomfort, but the shorter halflife of other SSRIs such as venlafaxine, paroxetine, duloxetine, citalopram, escitalopram, and sertraline (ranging approximately 10 hours) means that a single missed dose may cause withdrawal symptoms. When discontinuing an SSRI with a short half-life, switching to a drug with a longer half-life (e.g. fluoxetine or citalopram) and then discontinuing from that can decrease the likelihood and severity of withdrawal syndrome [12-14].

If one wishes to stop taking an SSRI medication, one method is to switch to a long half-life medication such as fluoxetine for several days at a relatively low dose and then stop taking any SSRI altogether. The longer half-life of fluoxetine will avoid any withdrawal symptoms because this medication effectively tapers itself from the patient's system over a few days.

SSRI withdrawal symptoms may be alleviated by either recommencing the original or lesser dose of the SSRI (or a similar SSRI), or slowly reducing the dosage over several weeks or months. While slowly reducing the dosage does not guarantee that a patient will not experience the discontinuation syndrome, it is considered a safer method than abrupt discontinuation. Gradual discontinuation, or tapering, or titration, can be accomplished by breaking pills into parts or using a graduated oral syringe with the liquid form. Alternatively, a compounding pharmacy may take one's prescription and divide it into smaller graduated doses. For example, a 20 mg prescription of Cymbalta, which comes in gel capsules containing tiny sphere-shaped pellets, may be divided into 20, 15, 10, 5, and 2.5 mg doses.

CONCLUSION

Treatment is dependent on the severity of the discontinuation reaction and whether or not further antidepressant treatment is warranted. In cases where further antidepressant treatment is required then the only step required is restarting the antidepressant; this is usually the case following patient noncompliance with the drug. If antidepressants are no longer required, treatment depends on symptom severity. Mild reactions may only require reassurance. Moderate cases may require symptom management. Benzodiazepines may be used for insomnia, although it's very important to note that benzodiazepine withdrawal is known to be severe and long-lived. If symptoms of SSRI discontinuation are severe, or do not respond to symptom management, the antidepressant can be reinstated and then withdrawn more cautiously.

People experiencing severe withdrawal symptoms may taper dosage by 5% per week (or month, or even longer) in order to avoid a drastic drop in serotonergic activity; however, even gradual reductions can produce withdrawal symptoms in some cases.

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