Rethinking Side Effects of the Selective Serotonin Reuptake Inhibitors:

Sexual Dysfunction and Weight Gain

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In the past decade, the selective serotonin reuptake inhibitors (SSRIs) have become the most widely prescribed antidepressant drugs. Over 80% of all new prescriptions for brand name antidepressants are written for fluoxetine, sertraline, paroxetine, and fluvoxamine. These drugs are extensively used because of their broad therapeutic spectrum, as reflected by FDA approval for the treatment of depression, panic disorder, and obsessive compulsive disorder. The early and continuing success of these drugs is also due to the marked contrast in safety and tolerability between them and earlier antidepressants, such as the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The safety and efficacy of the SSRIs has been underscored by the recent FDA approval of their use in children.

The clinical profiles of the SSRIs meet and in most ways exceed early expectations. There are no disabling or life-threatening adverse events that characterize these drugs. Our understanding of side effect patterns associated with use of these drugs has nevertheless changed over time. The frequencies of some adverse events differ from those reported in research studies. For example, gastrointestinal symptoms, decreased appetite, and activation were the most common side effects in premar-

keting studies, but are not as frequent or problematic as these trials suggested they might be. Only disturbances of sleep and daytime alertness seem to occur as predicted and to persist over time. On the other hand, several adverse effects that went virtually unreported during the clinical trial period have proven to be persistent and problematic. One of these adverse events, sexual dysfunction, has by now been widely discussed in the literature, and is considered to be a class effect of the SSRIs. Another treatment-emergent event that appears more commonly than predicted is weight gain. This latter effect has not been widely reported.

IMPORTANCE OF SIDE EFFECT RECOGNITION

The significance of these and other unexpected side effects is not that they occur. All drugs, especially those that act on the central nervous system, invariably cause some subjective side effects. The quality, severity, and probability of these side effects are often determinants of drug selection and a factor in patient acceptance of treatment. It is important to inform patients about possible side effects associated with a drug. Improved communication reduces the risk of a patient feeling misled or alarmed and helps to maintain trust and confidence in the physician should there be a need for change of medication or use of add-on medication. If side effects are not recognized as being drug-induced, they may be overlooked by the clinician, and the patient may thus needlessly endure the side effect. Proper recognition also results in more timely and effective intervention aimed at limiting the impact of a side effect on treatment outcome and quality of life.

One way to minimize the risk of treatment discontinuation is to assess a patient before prescribing a medication in order to determine
which side effects would be unacceptable, and chose a drug that carries minimal risk of causing those effects. Each of the newer antidepressants has a characteristic side effect profile, so that it is possible to select a drug based on the absence of a particular side effect. For example, several currently available drugs do not produce sexual dysfunction, significant sleep disturbances, or weight gain. Many side effects can be managed by using lower doses and slow upward dose titration. Some adverse events more typically require the addition of a second drug to offset the side effect. Sexual dysfunction and sleep disturbances associated with SSRIs, for example, are often managed with add-on therapy.

**TYPES OF SIDE EFFECTS**

Side effects are typically categorized by organ system involvement (eg, hematologic, nervous, renal) and frequency of occurrence (eg, frequent, infrequent, rare). The adverse events listed in the package insert reflect those that were documented during the acute clinical trials, which last 6 to 8 weeks. Short-term trials form the basis of FDA approval for new antidepressants, but most depressions are chronic and recurrent, and thus require ongoing medication. Inevitably, with clinical use, it becomes apparent that some side effects occur with much greater frequency than predicted by the premketing trials. Ironically, the awareness of long-term side effects may have become an issue with the SSRIs because their improved tolerability has meant that fewer patients discontinue treatment during the first weeks of treatment than with the MAOIs and TCAs.

**Early onset, time-limited side effects**

Acute side effects emerge at the outset of treatment, but abate or disappear with time. These are the adverse events that form the initial impression of a drug and lead to treatment discontinuation during the first month of medication. The most noteworthy examples of these are nausea, diarrhea, and activation. Most of the acute side effects are dose related, so they can be minimized by use of lower starting doses until tolerance develops. In fact, many clinicians now initiate fluoxetine at 10 mg/day or sertraline at 25 mg/day, doses that are one half the original starting doses.

**Early onset, persistent side effects**

Persistent side effects occur at the start and continue largely unchanged over time. Of all early onset SSRI-related side effects, sleep disturbances tend to persist over time. Of the gastrointestinal side effects, flatulence tends to persist more than nausea.

**Later onset side effects**

Some side effects do not emerge until weeks or months of treatment have elapsed. However, once they develop, these effects tend to persist. Because of their late onset and the absence of prominent mention in the product information, they often are not attributed to the drug. This is especially likely if the late manifestations are opposite to the acute effects. For example, a drug that initially causes activation and insomnia might not be suspected as the cause of somnolence. It is hard to determine the true onset of side effects over time, since early emergent effects might be obscured by the distressing symptoms of depression. As the depressive symptoms resolve, the side effects become more conspicuous. If weight gain occurs, and it is cumulative, it may not become problematic until it exceeds a patient’s traditional baseline weight.

**Withdrawal-emergent side effects**

Discontinuation of many types of psychoactive agents can result in withdrawal symptoms. TCAs, for example, have been associated with so-called cholinergic rebound symptoms. A highly distressing SSRI withdrawal syndrome consists of both physical and psychiatric symptoms. These commonly include dizziness, paresthesias, flu-like symptoms, anxiety, irritability, and tearfulness even in the absence of depressed mood. SSRI withdrawal symptoms emerge within 24 to 48 hours of discontinuing a rapidly eliminated SSRI, such as paroxetine, fluvoxamine, or sertraline. Withdrawal symptoms can also occur when dosage is reduced. It is possible that the fluoxetine withdrawal syndrome may be both delayed and attenuated by its long half-life and that of its active metabolite, so that discontinuation symptoms are mistaken for relapse of depression. Withdrawal effects do not occur unless an SSRI has been used for about 6 weeks.

Failure to diagnose withdrawal symptoms in clinical practice may result in unnecessary prolongation of treatment with an SSRI. The SSRI withdrawal symptoms are often misinterpreted as being a reemergence of the underlying disorder. The primary clinical significance of the SSRI withdrawal syndrome lies in the distress it causes the patients. Panic-stricken, agitated, tearful, these patients cannot comprehend why they feel so bad. Many primary care physicians are unaware of this side effect, do not counsel patients about the possibility of its occurrence, and do not routinely taper short half-life SSRIs.

**SEXUAL DYSFUNCTION**

By now, most clinicians are aware of the high incidence of sexual dysfunction associated with SSRI use. The unexpectedly high incidence of sexual disturbance, as manifested by orgasmic dysfunction and decreased sexual desire, has served to raise questions of whether other side effects were also underestimated. The original package insert for fluoxetine listed a sexual dysfunction rate of 1.9%. Since then it has been reported that the rate of secondary sexual dysfunction is between 40% and 50%, and perhaps substantially higher. One report of 60 consecutive male patients taking fluoxetine cited a rate of 75%.5
This relationship between the use of SSRIs and the occurrence of sexual dysfunction is clear, having been demonstrated in healthy volunteers as well as depressed patients. The adverse effects of SSRIs on sex occur almost immediately, but are not usually associated with treatment discontinuation early in treatment. While the patient is acutely depressed, sexual desire may be reduced already. Even if the patient continues to have normal sexual functioning during the depression, the dramatic relief of the depression may outweigh the impact of sexual disturbance. However, patients tend to become increasingly unwilling to accept this side effect once their depression has resolved.

Over time, some patients experience improvement in sexual functioning. A recent study found that difficulties with desire and psychological arousal in depressed women tend to remit, whereas the orgasmic dysfunction in males was common and persistent. Strategies such as dose reduction—sexual dysfunction caused by SSRIs is dose related—and brief drug holidays have been cited as ways to minimize orgasmic dysfunction. Short half-life SSRIs such as paroxetine are most likely to result in improved sexual response if they are withheld for 1 day. Add-on therapy with a broad range of pharmacologic agents has also been used.

In a study of 344 patients, Spanish researchers found a very significant increase in the incidence of sexual dysfunction when patients were directly questioned as part of systematic evaluation. In their study, the rate of spontaneous reports was 14.2% but the rate with a questionnaire was 58.14%, a nearly fourfold difference. There is no consistent finding of any differences in the incidence of sexual dysfunction among the drugs, although there is a suggestion that fluvoxamine causes the lowest incidence of sexual dysfunction among the SSRIs. All studies should be looked at critically because differences in dosing among the SSRIs may influence the likelihood of sexual dysfunction.

Mechanisms of Sexual Dysfunction: Nitric Oxide Hypothesis

Several hypotheses have been presented about why SSRIs produce orgasm-related sexual dysfunction. Most theories tend to focus on the role of monoamine neurotransmitters, most notably the dopamine and serotonin systems. None of these theories fully explain the underlying mechanism or mechanisms of sexual dysfunction, nor do they explain why numerous drugs with disparate synaptic effects have been reported to reverse these side effects. There is, however, emerging evidence that nitric oxide (NO) should be added to the list of agents that may mediate sexual function, and that alterations in NO activity may underlie some of the sexual side effects of the SSRIs.

Nitric oxide is a gas with free radical properties. It is not the same compound as the anesthetic agent nitrous oxide (N₂O). NO is synthesized by the conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). In the central and peripheral nervous system, NO regulates neurotransmitter release and plays a key role in synaptic plasticity and morphogenesis. It serves as a biological messenger and an effector molecule in signal transduction pathways in the autonomic nervous system, acts as a mediator of blood vessel relaxation, and is increasingly recognized as also mediating both physiologic and pathologic functions in the brain.

Although not realized at the time, the first clue linking NO to SSRI-associated sexual effects came from a case report that appeared shortly after fluoxetine was marketed in the United States. A letter appeared in the Journal of Clinical Psychopharmacology that described reactions in a female patient of spontaneous "yawning in the absence of drowsiness and multiple orgasms associated with clitoral engorge ment in the absence of voluntary sexual stimulation." The letter cited "an apparent causal relationship" between fluoxetine administration and these symptoms because the symptoms diminished over time but reappeared on dosage increase. The symptoms also disappeared when the fluoxetine was temporarily discontinued and reemerged when the medication was restarted. There is only one other published report that cites a case of fluoxetine-induced orgasms, this one in a male patient. Another case report describes a male who experienced excessive daytime yawning in the absence of sedation and who was able to have full erections but could not achieve orgasms. These cases have been widely referenced, but remain as a curiosity, since there have been so few subsequent reports of the yawning-orgasm syndrome.

There are earlier reports of other antidepressants causing this symptom complex. In 1983, McLean and colleagues reported four cases of patients taking clomipramine who experienced yawning alone, orgasms when they yawned, or irresistible sexual urges during "yawning spells." The authors of this report comment that they only discovered these side effects "coincidentally during routine side-effect queries" and that they "suspect that these side effects may not have been reported previously (particularly the phenomenon of orgasm) because of patient-unwillingness to reveal the experience." A later report described two cases of frequent yawning and sexual arousal caused by clomipramine. A female patient experienced orgasms with vaginal lubrication whereas a male reported a "hypogastric feeling of sexual pleasure."

Both yawning and sexual disturbance are listed as separate treatment-emergent events during clinical trials of the SSRIs. Yawning, surprisingly, is cited as a common side effect of the SSRIs. Up to 11% of fluoxetine- and 4% of paroxetine-treated patients were noted to have excessive yawning during clinical trials, whereas
none of those on placebo exhibited this symptom. There are no reports of spontaneous orgasm—alone or in conjunction with yawning—in the product information for any of the SSRIs, but there have been accounts of patients treated with SSRIs experiencing undesirable sexual arousal and hypersexuality in the absence of yawning. The highest rate of ejaculatory dysfunction noted in the product information for the SSRIs is 23%. Although the dysfunction is not specified, it presumably refers to problems in achieving orgasms.

Despite the paucity of case reports that describe SSRI-induced yawning and sexual arousal, an experimental syndrome of penile erections and yawning in animals is well documented. The results of this research point to the involvement of NO in both the animal models of sexual behavior and the clinically frequent sexual disturbances produced by SSRIs.

A group of Italian researchers have induced these symptoms in animals by injecting a variety of drugs and hormones into specific areas of the brain. Compounds that induce this yawning and sexual arousal include oxytocin, nitroglycerin, N-methyl-D-aspartic acid (NMDA), serotonin 5-HT₂₅c agonists (such as m-CPP), ACTH, and some dopamine agonists (such as apomorphine). The agents that produce this syndrome appear to have in common, except for their ability to cause penile erections and yawning. The researchers provide evidence, however, that NO plays an important role in both penile erection and yawning.

All these compounds, for example, increase production of NO in some way. Some of these agents, such as NMDA and oxytocin, have been shown to induce penile erections and yawning by increasing NO activity. Nitroglycerin on the other hand, acts as a NO donor.

Animal studies have shown that central and peripheral NOS is involved in the expression of male sexual activity. There is, for example, a direct relationship between male copulatory performance and NO activity in the paraventricular nucleus of the hypothalamus. NO mRNA expression in this nucleus in sexually potent rats is about twice that in sexually impotent rats. Almost all the research to date has involved the effects of NO activity in the central nervous system. However, testosterone, or one of its metabolites, plays a direct role in penile erection acting through a peripheral effect. Specifically, it acts on NOS within the corpora cavernosa. NOS appears to be dependent on testosterone. NOS inhibitors prevent the ability of the above noted agents to induce yawning and sexual behavior. Thus, in these experimental models, NOS inhibitors have an anti-sexual effect.

The possible link between these animal studies and the observed sexual effects of the SSRIs is that paroxetine and possibly other SSRIs act as potent NOS inhibitors. This has been demonstrated in vitro and in vivo in both humans and animals. So pronounced is the effect that NOS inhibition may account not only for sexual side effects, but may also impart positive therapeutic effects to the SSRIs. For example, it has been postulated that this property may help to reduce morbidity and mortality among patients who are depressed after a myocardial infarction. The relative contribution of NO inhibition to both the therapeutic and side effect profiles of paroxetine thus warrants further consideration.

In terms of managing sexual side effects, there may be a benefit to using agents that increase NO synthesis, perhaps through stimulation of NO. Dopamine agonists, such as dextroamphetamine and bupropion, for example, are reported anecdotally to both reverse SSRI-induced sexual dysfunction and promote NO synthesis. Studies using microdialysis in rats have shown that NO donors increase dopamine levels sixfold. Bromocriptine is also a dopamine agonist but it inhibits NO. Bromocriptine has not been reported to reverse SSRI-induced sexual dysfunction nor has it been noted to enhance sexual function in normal individuals. Clinical trials could be developed to see if dopamine agonists have differential effects on reversing SSRI-induced anorgasmia, depending on whether they activate NO (e.g., apomorphine) or inhibit NO (e.g., bromocriptine). m-CPP, a 5-HT₅c agonist that is a metabolite of trazodone and nefazodone, induces yawning and penile erections in rats. Nefazodone has been reported anecdotally to reverse SSRI-induced anorgasmia. NO precursors, including nutrients might be considered as possible therapeutic modalities as well. L-arginine is used in several therapeutic contexts, such as renal transplants and the treatment of metabolic alkalosis and warrants consideration as a treatment for orgasm-related disturbances. Similarly, nitroglycerine has been reported to rapidly and completely reverse the serotonin syndrome. The authors of this report hypothesize that the nitroglycerine acted as an “off signal” through nitric acid, thus counteracting the signs of the serotonin syndrome.

It should be noted that most of the animal studies of NO involve the injection of drugs directly into the central nervous system. The results of these methods cannot be extrapolated to clinical therapeutic modalities. The therapeutic effects of peripherally administered drugs also need to be studied. Some findings are not consistent. For example, yawning and penile erections can be dissociated. Multiple mechanisms may also be implicated. The speculation about the role of NO should thus be kept in perspective. Nevertheless, clinically oriented research may lead to more rational strategies for counteracting these side effects.

As a footnote, the prominent psychopharmacologist Donald Klein suggested at the time that Modell reported the case of fluoxetine-induced yawning-orgasm that "some idiosyncratic aspect of the patient's biology" rather than some class effect of the SSRIs accounted for the
symptoms.\(^{53}\) Klein also called attention to the similarity between these symptoms and erections and yawning seen during opiate withdrawal. Perhaps, he noted, there is a similar underlying mechanism. Klein speculated that opiate withdrawal symptoms and SSR1-induced yawning and effects may be mediated by a common mechanism. In fact, research evidence suggests that NO mediates the effects of morphine on erection and yawning.\(^{45}\) Morphine is known to prevent erections and yawning that is induced by administration of apomorphine and oxytocin, and might conceivably cause these effects as part of an opiate withdrawal syndrome. Results from a recent study show that morphine acts through mu receptors in the paraventricular nucleus to prevent induced penile erection and yawning and suggest that this morphine effect is mediated by a decreased activity of NO in this area of the brain.\(^{46}\) An apparently accurate hypothesis is a reminder that many advances in psychopharmacology are the result of informed clinical observation.

**WEIGHT GAIN**

Clinical trial data predicted little liability of SSRI-induced weight gain. The incidence reported in the product information for these drugs is extremely low. Yet, in clinical practice many patients exhibit excessive and unwanted increases in body weight. There are few mentions of weight gain associated with SSRIs in the basic science or clinical literature. An increase in weight from baseline of 7% or more is considered to be clinically significant and is the standard used in clinical trials.

The limited information on SSRI-related weight gain involves treatment periods that range from 6 weeks to more than 12 months.\(^{54,55}\) Reports on the incidence of weight gain in patients treated with fluoxetine ranges from less than 1%\(^ {56}\) to as much as 50%.\(^ {67}\) The only report of weight gain among fluoxetine-treated inpatients, a retrospective chart review of patients treated for several weeks or months, describes weight gain in 30% of patients.\(^ {58}\) Amsterdam and colleagues conducted a study of 59 women treated with fluoxetine, sertraline, paroxetine, or venlafaxine for 2 months or more.\(^ {67}\) Fifty percent of the women gained weight. The study was primarily intended to determine if these drugs caused breast enlargement. The investigators found that 39% of patients reported some breast enlargement. Of these, 64% of women taking paroxetine, versus 25% of fluoxetine, 25% of sertraline, and 11% of venlafaxine reported breast enlargement. Weight gain occurred in 84% of the women with mammaplasia versus 30% without mammaplasia. A significant increase in prolactin was associated with paroxetine therapy.\(^ {67}\)

Patterns of weight change while taking SSRIs are determined by duration of therapy. Early treatment with SSRIs is known to be associated with weight loss in some patients, but over time, almost all of these patients regain this weight. Contrary to what is understood by most physicians, SSRIs produce less weight loss than is generally appreciated. Comparative antidepressant trials involving 333 patients treated with fluoxetine found that the average weight loss over a 6-week period was two to four pounds.\(^ {69}\) Weight loss with fluoxetine, when it occurs, peaks at about 20 weeks, and on average weight begins to be regained after 6 months. At the end of 1 year, there is no significant decrease in weight. Similarly, sertraline was investigated as part of a controlled trial of relapse prevention training in the maintenance of weight loss.\(^ {70}\) A similar pattern has been found with sertraline. During the first 6 weeks, sertraline subjects lost significantly more weight and reported significantly greater reductions in hunger and preoccupation with food than did subjects on placebo. After this time, however, the sertraline and placebo patients regained weight steadily. A summary of long-term paroxetine trials involving patients treated for more than a year found that 18% gained 7% or more of their baseline weight.\(^ {71}\) Typically, patients notice the onset of weight increase after several weeks or months of treatment. It may start early in treatment but go unnoticed until significant weight has been gained.

Mean increases of about 20 pounds are reported in the literature.\(^ {61}\) We have encountered patients without a prior history of being overweight who have gained up to 40 pounds while being treated with SSRIs. In one study, the mean weight gain of those who gained weight on fluoxetine was 9.6 kg (21.1 pounds), whereas those on sertraline gained 6.9 kg (15.3 pounds).\(^ {54}\) The clinical trial data for patients on paroxetine for more than 1 year described an average weight gain of 11 kg (24 pounds). There were no placebo controls in the previous studies. In a case series of six patients treated with fluoxetine for a mean duration of 9.8 months who experienced weight gain, the mean weight gain was 20 pounds.\(^ {61}\) In a citalopram case series involving 5 weeks of treatment, weight gain ranged from 4.8 kg to 11 kg (average of 15.7 pounds or 7.1 kg).\(^ {62}\)

**Possible Causes of Weight Gain**

The mechanisms by which SSRIs affect body weight are complex and not well understood; many distinct mechanisms can influence body weight. In general terms, they either alter caloric intake or modify energy expenditure or both. Drugs can alter caloric expenditure by increasing or decreasing the basal metabolic rate without changing caloric intake. There is even one report of a fluoxetine-treated patient who lost a large amount of weight while experiencing a marked increase in food intake.\(^ {63}\)

It seems paradoxical that SSRIs should cause weight gain, since animal studies suggest that acute SSRI use results in an increase of the metabolic rate. A 2-week study of fluvoxamine, for example, found a 26% to 40% increase in the metabolic rate.\(^ {64}\)
It is generally held that drugs, such as the SSRIs, that increase the output of serotonin decrease hunger and food intake. Conversely, decreased serotonin transmission results in hunger and increased food consumption.65 These effects probably result from stimulation of post-synaptic serotonin receptors.

The most commonly offered rationale for weight gain during SSRI therapy is that it represents normalization of weight that was lost during the depressive episode. Major depression often reduces appetite and body weight. By restoring appetite, SSRIs can cause an increase in weight. Arguing against this is the fact that patients who take SSRIs for the treatment of panic disorder and obsessive disorder, conditions not associated with significant weight loss, also experience unexpected weight gain.61 In addition, there need not be a relationship between clinical response and weight gain.

In most reported cases, weight gain does not appear to be attributable to concurrent use of other medications. However, some of the observed weight increases among patients taking SSRIs may result from concurrent use of benzodiazepines. According to some studies, about one third of patients treated with SSRIs are also receiving an anxiolytic or hypnotic. Benzodiazepines have been observed to cause weight gain and to stimulate appetite.65,66

A more recent study involving 17 male research volunteers, for example, found that alprazolam significantly increases total daily caloric intake by about 25%—from about 2800 kcal to about 3800 kcal.67 Patients gained about 4 pounds. Alprazolam (0.75 mg twice a day) increased the frequency and amount of eating. Most of the additional eating took place at night. Findings suggest that there is direct and indirect involvement of SSRIs and the 5-HT_2 receptors.68 The reason that the 5-HT_3 receptor is important in terms of weight from accumulating evidence that these receptors may serve as part of the body’s fat control system.69 A series of sites found in the mRNA encoding the 5-HT_2 receptor serve as targets for the RNA adenosine deaminases that are involved in regulating weight.70 Mice that have been bred to be devoid of 5-HT_2 receptors invariably have an eating disorder and are obese.71 In addition, 5-HT_3 receptor agonists, such as m-CPP, are not able to act as appetite suppressants in these mice. In both animal and human studies, m-CPP is typically associated with decreased appetite and weight loss. Citalopram, fluoxetine, and fluoxetine’s metabolite norfluoxetine and its R-enantiomer may influence 5-HT_3 receptor regulation by binding to those receptors.72 Each of these compounds has a 23-fold selectivity for the 5-HT_3 receptor over the 5-HT_2A receptor. Sertraline does not have significant binding to either of the receptors. Ni and Miledi73 have more recently reported that fluoxetine rapidly and reversibly inhibits the binding of serotonin to these receptors in HeLa cells and in rat cortex as well as the responses of 5-HT_3 receptors to serotonin. The researchers concluded that some of the therapeutic effects of fluoxetine might involve blockade of the 5-HT_3 receptors, as well as reuptake blockade.

Chronic SSRI treatment also has been reported to indirectly attenuate the function of 5-HT_3 receptors. Repeated administration of SSRIs decreases responsiveness of central 5-HT_3 receptors.74,75 This was demonstrated by measuring the effect of SSRIs on m-chlorophenylpiperazine (m-CPP)-induced behavior and neuroendocrine responses. (The antidepressants trazodone and nefazodone undergo oxidative cleavage to yield m-CPP. This metabolite is a potent 5-HT_3 and 5-HT_2A agonist that is used as an experimental probe of the serotonin system.)

An additional possibility is that the initial decrease in food intake experienced by some patients may cause changes in the sensitivity and affinity of serotonin reuptake transporters. Young rats subjected to significant food restriction for up to 2 weeks exhibited a reduction of about 30% decline in the density of serotonin transporters in the cortex.76 These changes were not observed in older animals. In fact, the authors make special note of the fact that these phenomena disappear with increasing age. Of interest is the fact that elderly humans also seem less sensitive to the effects of SSRIs on weight than younger adults do. Patients who gained weight, according to one study, had been on an SSRI for extended periods and were disproportionately younger than 60 years of age.65

Dopamine activity is involved in the regulation of metabolism. Dopamine agonists, such as bromocriptine, reduce body fat stores and improve carbohydrate and lipid metabolism without significantly altering food consumption.64 Drugs that directly block D2 receptors, such as haloperidol and chlorpromazine, produce weight gain. SSRIs have been shown to decrease dopamine turnover indirectly via the effects of serotonin projections on dopamine neurons. The study of breast enlargement during SSRI treatment, for example, found that increased prolactin levels were associated with breast mammoplasia and weight gain in women treated with paroxetine, which has the most potent and selective effect on serotonin reuptake.57

Histamine receptors in the hypothalamus also mediate appetite, and H1 antagonists are known to cause weight gain through stimulation of appetite. Cyproheptadine, a H1 and 5-HT_2A antagonist, is used for this purpose among patients who are seriously underweight. As a rule, SSRIs are not potent antihistamines. Citalopram, however, has a marked affinity for the H1 receptor, and in one case series, produced increased craving for carbohydrates early in treatment. Both the early effect and carbohydrate craving are not characteristic of the other SSRIs. Antidepressants can have metabolic and appetite effects through other systems that are independent of monoamine neurotransmitters.
Peptides, for instance, have some effect on hypothalamus, an important control center for metabolism. Antidepressants alter caloric expenditure by increasing or decreasing the basal metabolic rate without changing caloric intake. Similarly, lipogenesis may somehow be altered. The effects of fluoxetine on appetite, for example, have been found to be independent of serotonin synaptic function and mediated by an additional unknown mechanism.

Thus, despite the limited body of literature, there is evidence that weight gain is a class effect of the SSRIs. In most of the reported cases and in clinical experience, the increased weight is not linked to a subjective awareness of increased caloric intake. Consistent with this pattern is the ineffectiveness of exercise and diet as measures to lose weight. Weight gain, when it occurs, develops after long-term treatment and is likely to be greater and more persistent than weight loss that occurred initially, either as a result of the depression or the early anorexic effect of the SSRIs. As with other side effects, there is a suggestion that the SSRIs are more likely to cause weight gain than others are. Comparative risk of weight gain among the SSRIs cannot be estimated with certainty due to the lack of data.

CONCLUSIONS

The SSRIs are important drugs. They have a broad spectrum of activity and are widely prescribed. Because of their extensive use, accurate knowledge of their side effects—how to avoid them and how to manage them once they emerge—represents an essential aspect of clinical skill, especially for psychiatrists. There has been a growing realization that reliance on information provided in the product information leaflets results in only partial understanding of the adverse events profiles for these drugs. Some SSRIs side effects are more common than initially suggested. The exact incidence of sexual dysfunction and weight gain is not known, but by some accounts, the figure for each probably exceeds 20% of SSRI treated patients. Increased body weight and sexual dysfunction each represent a physiologic change associated with a low threshold of acceptability. As a result, they have a disproportionate impact on overall patient satisfaction with treatment and are generally incompatible with long-term medication compliance.

Some of the adverse effects reviewed above may have been underreported and underestimated during clinical trials because they typically emerge beyond the time frame of the trials. Most subsequent awareness of these effects has come from uncontrolled studies and case reports. Some side effects were not explicitly assessed during clinical trials. This was certainly true during fluoxetine trials in terms of sexual functioning. Another possibility is that subjects in clinical trials are not representative of those in the treatment population. Their prior exposure to multiple medications might have made them more tolerant to side effects than other patients. Whatever the reasons, sexual dysfunction and weight gain are common and problematic among SSRRI-treated patients. They can be managed in some cases through changes of dosage and the addition of other medication. The exact incidence, cause or causes, and optimal management of each of these side effects need to be determined. One potential outcome from studies of these side effects is that this research may reveal the underlying physiological mechanisms that mediate drug effects on appetite and sexual functions.

REFERENCES


