Persistence of Sexual Dysfunction Side Effects after Discontinuation of Antidepressant Medications: Emerging Evidence

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Abstract: Post-market prevalence studies have found that Selective Serotonin Reuptake Inhibitor (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) sexual side effects occur at dramatically higher rates than initially reported in pre-market trials. Prescribing and practice conventions rest on the untested assumption that individuals who develop sexual dysfunction secondary to SSRI and SNRI antidepressant medications return fully to their pre-medication sexual functioning baseline shortly after discontinuing treatment. Most individuals probably do return to their previous level of sexual functioning, however recent case reports, consumer-provided Internet-based information, incidental research findings, and empirical evidence of persistent post SSRI sexual benefits in the premature ejaculation literature suggest that for some individuals, SSRI and SNRI-emergent sexual side effects persist indefinitely after discontinuing the medications. The literature poorly captures the full spectrum of SSRI/SNRI sexual side effects, and a lack of systematic follow-up in the sexual side effects research precludes detection of post SSRI/SNRI sexual dysfunction, leaving the formal knowledge base inadequate and even inaccurate, raising informed consent issues, and leaving clinicians vulnerable to practicing in ways that may be hurtful to patients in spite of their best efforts to inform themselves.

Key Words: SSRI, iatrogenesis, persistent sexual side effects, sexual dysfunction, genital anesthesia.

INTRODUCTION

The present article discusses issues and evidence related to sexual side effects of selective serotonin reuptake inhibitors (SSRIs) including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox), and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor)[1]. Sexual side effects are known to occur as a result of drug treatment, but their prevalence is underestimated in the product literature, and the research literature poorly captures the quality and scope of the sexual side effects and how distressing they may be to patients.

The SSRIs and SNRIs are approved and considered first line treatments for depressive disorders, generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, bulimia, premenstrual dysphoric disorder, and post traumatic stress disorder. Increasingly, they are prescribed off-label [1] to treat conditions such as peri-menopausal and post-menopausal hot flashes, chronic fatigue syndrome, chronic pain syndromes, premature ejaculation, and paraphilias. In the latter two conditions, the sexual side effects are intended as the primary and desired effects.

Recent estimates are that on average, 43% of patients seen by psychologists take medication adjunctively to psychotherapy [2], and that one in eight adult American has taken an SSRI or SNRI over the last ten years [3]. In the present author's practice setting at a large university counseling service, nearly fifty percent of the generally high-functioning and sexually active or sexually motivated young adult clientele are taking psychotropic medications, usually SSRIs or SNRIs [M. Harris, Clinical Director, University of Iowa Counseling Service personal communication, Dec.5, 2007]. There is a growing consensus that psychologists need to be knowledgeable about psychotropic medication effects and side effects as a competency issue and a standard of care [4]. Given mental health professionals' responsibility for client welfare, when clients are taking or are contemplating taking SSRIs/SNRIs, psychologists have an obligation to inform clients of the possibility of sexual side effects, and in collaboration with clients and prescribing professionals, to consider the impact of adding a new, medication-related sexual dysfunction to the client's condition. Prescribing psychologists are optimally positioned to monitor and to be responsive to treatment implications of emergent medication side effects [5] .

The possibility that treatment-related sexual side effects may persist in some patients after stopping the medications seems to be unrecognized among the research and professional communities, yet is increasingly identified among Internet communities [e.g. SSRIsex@yahoogroups.com; http://www.sexual-dysfunction.info/forum/], and described in a series of recent case reports [6-9]. My immersion in the formal literature, in my clinical practice, and in consumer-based Internet information has led me to believe that the existing knowledge base with regards to SSRI/SNRI sexual side effects is unintegrated, inadequate, and even inaccurate, raising concerns about informed consent, and leaving clini-

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[1] Sexual side effects of the SNRI duloxetine (Cymbalta) are less well-studied.

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cians vulnerable to unknowingly contributing to iatrogenic harm.

The present article presents available evidence indicating that SSRI and SNRI-emergent sexual dysfunctions, for an unknown number of patients, may not resolve upon cessation of medication. As discussed in Rivas-Vasquez, Rey, Blais, *et al.* [5], sorting out the etiology of sexual dysfunction can be challenging. Evidence considered in the present article is confined to sexual dysfunctions that were not present at baseline, and emerged only with drug initiation, maximizing the probability that the dysfunction is drug-induced. Evidence presented comes from a variety of sources including incidental research findings, empirical findings, case reports, and consumer-reported experiences. In addition, two distinctive sexual symptoms are highlighted that are rarely reported in the research literature, but are often identified as among those symptoms that persist after treatment discontinuation in both case reports and among members of an Internet community. It is proposed that these unusual symptoms, genital anesthesia and anhedonic orgasm/ejaculatory anhedonia (i.e. diminished or absent genital- tactile sensitivity and orgasm or ejaculation that is not associated with physical sensations of pleasure), often missed by our assessment instruments, may serve as lingering markers of past SSRI or SNRI exposure [10], further helping to distinguish medication effects from sexual dysfunctions that may be primarily of psychological origin.

Searching the data bases of research studies yielded no published investigations that bear directly on the problem of persistent sexual side effects after discontinuation of SSRIs/ SNRIs. With few exceptions, the research investigating SSRI/SNRI sexual side effects has not included follow up after discontinuation of the medication. However a number of investigations, not primarily motivated by concern about long term drug safety, have followed SSRI-emergent sexual side effects for a six month period after discontinuation of the medications [11-13]. The researchers did not interpret their findings as raising concerns about the persistence of sexual side effects after discontinuation of SSRIs, but such alternative interpretations of the findings will be discussed.

UNDERESTIMATION, MINIMIZATION, AND GAPS IN KNOWLEDGE ABOUT SSRI/SNRI SEXUAL SIDE EFFECTS

Post market research has clearly established that the SSRIs and SNRIs can affect most every aspect of sexual functioning at rates significantly higher than the 2-16% rates reported in pre-market trials and currently listed in the drug insert literature. Large prospective studies in which baseline assessment excludes participants with pre-existing sexual dysfunction have found rates of treatment-emergent sexual dysfunctions such as decreased libido, delayed orgasm, anorgasmia, erectile dysfunction, and difficulties with arousal, of between 36 and 70% [14, 15]. The 2-16% pre-market rates of SSRI and SNRI-induced sexual side effects are based on spontaneous reports of individuals in initial trials who had been on the medications a short time. When individuals are directly and systematically asked about changes in sexual functioning via a structured clinical interview or a self-report inventory, dramatically higher rate information is obtained as compared with reliance on individuals to spontaneously volunteer personally sensitive information about changes in sexual functioning [15, 16].

Current American Psychiatric Association treatment guidelines do not recognize clinically significant differences in efficacy among the various medications [17]. The choice to prescribe one SSRI or SNRI over another is often based on the known side effect profile, with the reported impact on sexual functioning often a deciding factor [18]. While sexual side effects are probably the most-researched of all the SSRI and SNRI side effects, the foci, motivated by competing drug companies' efforts to gain a market share, have been heavily on: determining the comparative prevalence rates of a variety of sexual side effects; determining strategies for managing the sexual side effects: demonstrating the efficacy of one medication to serve as an antidote to the sexual dysfunction caused by another; and also on the ejaculation-delaying benefits of the various SSRIs when used as an off-label treatment for premature ejaculation (i.e. see Waldinger [19] for a review).

Despite the substantial body of literature devoted to comparative sexual side effects prevalence rates and antidotes, there is little indication of clinically significant differences among the medications with regards to rates of associated sexual side effects [20] and no strategy or antidote has proven reliably effective for alleviating the SSRI or SNRI-induced sexual side effects. While the consistent impression given by the literature is that sexual side effects may be easily resolvable in consultation with the prescriber, the management of antidepressant sexual side effects, according to Balon [16], should currently be seen as an art and not a science. An estimated 5 to 10% of individuals may experience a diminution of the SSRI or SNRI emergent sexual side effects over time as they remain on the medication [21], but for the vast majority, the sexual side effects are intractable and will continue for at least as long as they take the medication [14, 15].

The research questions related to SSRI/SNRI sexual side effects that are of most interest to industry sponsors are not the same questions that are of most interest and urgency from a public health perspective. As a result, important gaps in knowledge remain. These gaps include, but are not limited to: 1) Information as to which sexual side effects are most characteristic of the SSRIs/SNRIs; 2) The degree to which side effects remain stable or change over the course of longer term treatment; 3) When and whether individuals who develop sexual side effects secondary to the medications return fully to their pre-medication sexual functioning baseline; 4) What impact the medications may have on fertility and reproductive health, and; 5) In what ways the medications may affect the developing sexuality of adolescents and children. Gaps 1, 2, and 3 will be explored more fully in this article.

While the potential impacts of SSRIs and SNRIs on fertility and reproductive health, and on adolescents' developing sexuality are beyond the scope of this article, there are reasons to be concerned: Tanrikut and Schlegel [22] recently found SSRI usage in two men to be related to impaired semen parameters, which apparently improved when the men discontinued the medications. And Scharko [23] notes that while sexual side effects may be expected to occur in adoles-

cents at rates similar to those found in adults, his review of the adolescent SSRI literature found a nearly complete lack of information or research related to SSRI sexual side effects in adolescents, and no developmentally appropriate instruments for assessing the medications' impact on adolescent sexual functioning.

The assumption of a sexual-functioning return to baseline shortly after cessation of the medications is deeply embedded in the literature, as well as in the conventional approach to practice and prescribing [10]. Yet no primary source was found to substantiate the resolution of sexual side effects: no study was found that systematically and intentionally followed the course of SSRI or SNRI-induced sexual dysfunction after discontinuation of the medications for the drug-safety-related purpose of determining when and to what degree the sexual side effects resolve. A search of the literature resulted in identifying only a single study in which fluoxetine-emergent sexual side effects were reported to have resolved within one to three weeks of cessation of medication [24]. The author does not specify when or by what means the follow-up information was obtained or how many of 54 patients in this two-year, naturalistic, private-practice based study had discontinued the medication and were available for follow up. Treatment-emergent sexual side effects probably do resolve for most individuals after discontinuing the medications, yet since sexual side effects might persist after treatment cessation for *some* individuals, researchers have an obligation to design studies so as to assess this likelihood. In the vast majority of studies of SSRI sexual side effects, no post-treatment follow-up is included in the research protocol, and/or participants are still actively taking the medication at study endpoints.

The SSRI/SNRI sexual side effects literature generally reflects the perspective that the sexual side effects pose a threat to treatment compliance [i.e. 30, 37, 43]. Indeed, it is believed that up to two-thirds of patients discontinue a guidelines-recommended course of antidepressants due to adverse events, particularly sexual dysfunction [25]. Less frequently mentioned, or only perfunctorily treated is the responsibility of prescribing professionals to address the interaction of a new or worsening sexual dysfunction with the condition being treated, and the impact on general quality of life in the collaborative negotiation of treatment alternatives. The failure of the SSRI-research literature to fully engage in addressing the psychological costs of medication-induced sexual dysfunction suggests that clinicians may sometimes fail to invite fully collaborative interactions in response to patients' concern about SSRI-emergent sexual dysfunctions. Instead, they may engage in something more akin to what Higgens *et al.* [26] describe as a "compliance monologue"[p. 441] motivated by, among other things, the professional's own discomfort with initiating an in-depth conversation about sexual functioning, bolstered by an a priori allegiance to a pharmacological model of treatment.

In response to individuals who express concern about treatment-emergent sexual side effects, clinicians are advised to reassure patients that the side effects are "medically benign" [27 p. 23] and that " all data suggest return of sexual functioning to baseline once the medication is stopped" [28 p. 106]. The conventional wisdom seems to dismiss even the possibility that sexual side effects may continue after stopping the medications by defining true drug-induced sexual dysfunction as, "that which occurs after the agent is started or the dosage is increased, is not partner-specific, is not lifelong or recurrent, *and resolves when drug therapy is discontinued*" (italics added) [29, p. 825]; or, that which " is not better explained by physical illness or stress, whose onset is with drug initiation or dose increase, is present in all sexual situations, reappears with reintroduction of the drug, and *dissipates with drug discontinuation or dose reduction*" (italics added) [30, p. 1489].

The assumption of benignness, along with such intuitively attractive, yet empirically untested definitions of drug-induced sexual side effects, contributes to the systematic failure to include post-treatment follow-up in our research designs. These assumptions also underscore the reasons that clinicians, and even patients themselves may fail to consider past SSRI or SNRI medication use as a possible cause for otherwise unexplained persistent sexual dysfunctions. Current definitions are unsatisfactory, as they do not allow for the possibility that sexual side effects that begin on medication and persist after medication discontinuation could be medication-related.

GENITAL ANESTHESIA AND PLEASURELESS ORGASM: UNCOMMON OR CHARACTERISTIC OF SSRI/SNRI SEXUAL SIDE EFFECTS?

There are indications that some SSRI/SNRI sexual side effects thought to be rare are actually common [10]. The most frequently documented sexual side effects are diminished libido, unspecified problems with arousal, and delayed orgasm or anorgasmia. Delayed ejaculation or orgasm, and anorgasmia have been those symptoms that the literature links most clearly and most frequently to SSRI treatment, vs. to depression itself [16]. However the symptoms of genital anesthesia and pleasureless orgasm, outside the range of common experience and appearing to often occur together, are frequently reported among men and women in Internet communities, in an accumulating case reports literature [6-9, 31-36], and in one research investigation [37].

These counterintuitive symptoms can be described as a preservation of aspects of normal physical sexual functioning, but with a loss of the concurrent capacity to experience sexual pleasure or arousal. Genital anesthesia has been described in Internet forums and in case reports as genitals that are numb or nearly numb, which may respond to stimulation by erection or lubrication, but without attendant subjective feelings of arousal. Pleasureless orgasm or ejaculatory anhedonia can be described as orgasm or ejaculation that is preceded by little sense of building arousal, is identifiable by rhythmic perineal muscle contractions in women or by ejaculation in men, but is experienced as pleasureless or nearly so. These qualitatively different symptoms are not easily classifiable in regard to any specific category of the sexual response cycle, and as Bahrick has noted, elude capture in most prevalence studies [10]. Decreased orgasmic intensity or ejaculatory anhedonia are not mentioned in recent reviews of disorders of ejaculation and orgasm in men [38], or in women [39], and SSRI/SNRI-related decreased genital sensitivity or genital anesthesia, when mentioned, are reported to be uncommon [6, 14, 15]. However it is more accurate to say that the symptoms are uncommonly assessed.

Michael and Mayer [32] describe a case of fluoxetine-induced anesthesia of the vagina and nipples in an initially depressed woman who had experienced lowered libido concurrently with depression. Michael and Mayor linked her genital and nipple anesthesia to the treatment and not to the patient's condition, as the anesthesia persisted even when the initially depressed patient became euthymic. Deisenhammer and Trawoger [36] demonstrated with a re-challenge test that genital anesthesia was indeed caused by treatment with citalopram in the case of a 36 year old man treated with citalopram for an adjustment disorder with depressed mood. The man, reported not to have any preexisting sexual dysfunctions, experienced penile anesthesia after three days on the medication. The symptom resolved shortly after stopping the medication, which he'd continued for three weeks due to its mood lifting effect. A year later, the man, described as healthy and with no mood or sexual difficulties, consented to re-exposure to citalopram. He again experienced penile anesthesia after several days on citalopram, which again resolved several days after stopping the medication.

Deisenhammer and Trawoger [36] state that genital anesthesia is probably associated with all antidepressants that enhance serotonergic neurotransmission. Clayton and Montejo [21] point to a possible basis for the symptom, noting that serotonergic medications may decrease genital sensation via diminished nitric oxide function. Nitric oxide is integral to penile and clitoral tumescence. Deisenhammer and Trawoger [36] call for controlled studies to evaluate the incidence of SSRI induced genital anesthesia. To the present author's knowledge, no such controlled studies have been performed. Indeed, our literature supports the assumption that genital anesthesia and ejaculatory anhedonia/pleasureless orgasm are rare by failing to systematically include the symptoms in our instruments, and by failing to report them transparently when they are included [10].

According to Clayton and Montejo [21], The Changes in Sexual Functioning Questionnaire (CSFQ) [40], and the Arizona Sexual Experiences Scale (ASEX) [41], are the primary validated instruments used to assess sexual dysfunction secondary to psychotropic medication. Neither the CSFQ nor the ASEX include specific queries related to changes in genital sensitivity. And neither unambiguously captures pleasureless orgasm or ejaculatory anhedonia; the CSFQ fails to do so by scoring decreased orgasmic intensity together with items assessing timing and frequency of orgasm, and the ASEX because the inquiry regarding changes in satisfaction from orgasm is less specific than changes in intensity of orgasm.

To the present author's knowledge, the Rush Sexual Inventory is the only instrument, validated in 2005 [42], for assessing medication-related sexual changes that includes specific queries related to both changes in sensitivity of external genitalia as well as changes in orgasm intensity. However, as items are answered in a yes/no format, the instrument captures the presence, but not the severity of the symptoms. Two studies were found that assessed SSRI-related sexual side effects using the Rush Sexual Inventory: Ferguson [43] did not report specific symptom results, and Zajecka *et al.* [37] reported only partial results. Zajecka *et al.* [37] found that among 42 depressed patients taking a variety of SSRIs, 28% of women reported treatment-emergent decreased genital sensitivity and 25% of men reported treatment-emergent decreased intensity of orgasm, suggesting the symptoms are not uncommon. While data were collected for both genders for both symptoms, results were reported for only one of the symptoms for each gender. The article's abstract notes the Rush Sexual Inventory's utility for follow-up assessment, however no follow-up data were provided regarding the resolution of the SSRI-induced sexual side effects.

Genital anesthesia and pleasureless orgasm or ejaculatory anhedonia should be of special interest to both researchers and clinicians. The symptoms are unknown in the general population, are not known to be associated with any conditions or disorders for which SSRIs or SNRIs are prescribed, yet seem to be distinctive markers of medication treatment. When treatment-emergent sexual side effects persist after discontinuing SSRIs or SNRIs, patients' reports may be discounted, disbelieved, ascribed to a relapse of the presenting problem, or to the emergence of yet a new mental health problem by professionals to whom individuals turn for help. Thus, Bahrick has suggested that among all the sexual side effects that may emerge during treatment or persist after cessation, genital anesthesia and ejaculatory anhedonia may provide the most compelling links to the *treatment* rather than the conditions being treated [10].

EVIDENCE OF PERSISTENT SEXUAL SIDE EFFECTS AFTER DISCONTINUATION OF SSRI/SNRI MEDICATIONS

An Incidental Finding

Montejo *et al.* [11] appear to have found incidental evidence of SSRI-induced sexual side effects continuing after cessation of the medication. The study's aim was to assess the impact of changing to another medication in patients whose depressive symptoms had successfully remitted with a variety of SSRIs, but who had developed treatment-emergent sexual dysfunction. Patients were switched either to amineptine (n=47), an atypical tricyclic antidepressant that is no longer available, or to paroxetine (n=38). A third group of depressed patients was treated with amineptine only (n=26) and had no prior SSRI treatment. All three groups were followed with multiple assessments over a six month period.

Montejo *et al.* [11] report for those patients taking amineptine only, amineptine was not a cause of secondary sexual dysfunction, and also effectively treated depressive symptoms. In the group switched to amineptine, the incidence of sexual dysfunction dropped from 100% to 55% over the six month period, while depressive symptoms remained in remission. In the group switched to paroxetine, sexual dysfunction decreased only slightly from 100% to 89.7% after six months. The authors interpret these findings to support with high confidence ($p<.001$) the conclusion that amineptine is an effective antidepressant that is able to significantly improve the SSRI-caused sexual dysfunction, yet maintain the efficacy of the antidepressant treatment used before. An alternative interpretation is that for 55% of individuals switched to a medication that successfully treated depressive symptoms and was not a cause of secondary sexual dysfunction, the initial SSRI-induced sexual dysfunction persisted for at least six months after discontinuing the SSRI [10].

Empirical Evidence: Persistent Sexual Benefits after Discontinuation of SSRIs

The well-established ejaculation-delaying effects of all of the SSRIs has led to their ubiquitous off-label use as a treatment for premature ejaculation (PE), and motivated industry to seek approval of SSRIs for a new indication reported to affect approximately 30% of men globally across all age groups [44] and to affect up to 70% of men at some point in their sexual lives [45]. The large emerging literature related to SSRIs as a treatment for PE asks which SSRIs may have the longest or most potent ejaculation-delaying effect; whether chronic or on demand administration of SSRIs is preferable and in what dose, whether newer shorter-acting SSRIs may prove more efficacious than those already on the market, and *whether the medications may provide lasting benefits beyond treatment discontinuation*. With current in-the-field practice moving well ahead of demonstrated long-term safety, a recent survey of urologists indicated SSRI treatment is the most common first-line approach to managing premature ejaculation [46].

Two recent studies found robust evidence for sustained post-treatment effects of SSRIs on ejaculation latency [12, 13]. Safarinejad and Hosseini [12] evaluated citalopram as a treatment for PE in a prospective, double-blind, placebo controlled, fixed dose (20 mg.), randomized study of fifty-eight non-depressed, psychologically and physically healthy men whose only sexual complaint was PE. Premature ejaculation was defined as intravaginal ejaculatory latency time (IVELT) of less than two minutes in more than 90% of coitus. The impact on sexual functioning of the citalopram (n=29) and placebo (n=29) treatments was assessed every two weeks during the twelve-week treatment period, and in three and six month follow-ups after cessation of treatment. Safety and efficacy measures included: changes in IVELT which subjects recorded with a stop watch; frequency of intercourse, adverse drug events which subjects recorded in an apparently open format diary, and the use of a subset of six out of fifteen questions from the International Index of Erectile Function (IIEF) reflecting a domain of "intercourse satisfaction".

The authors report significantly improved ejaculation latency (IVELT) scores ($p<.001$) for the citalopram group vs. the placebo group beginning at week one and continuing throughout the 12-week treatment phase, and improved intercourse frequency as well as satisfaction in the citalopram group over the placebo group ($p<0.05$) by week 12. They report no adverse treatment-related changes in erectile function for the treatment group, or any negative impacts on any aspect of sexual functioning. And, astonishingly, Safarinejad and Hosseini found the significant ejaculation delaying benefits in the citalopram group to be robustly sustained ($p<.001$) after discontinuing the medication in both the three and six month follow-up assessments. The authors offer a biologically-based hypothesis regarding the ejaculation delaying benefits of citalopram, and conclude that "the real, long term efficiency of citalopram was proved after treatment cessation" [12 p.169].

Arafa and Shamloul [13] evaluated sertraline, (50 mg.), as a treatment for PE in a large, prospective, single-blind, placebo-controlled, crossover study of 147 healthy men. Premature ejaculation was defined as ejaculation that occurred within two minutes of vaginal intromission. Included in the study were men who met criteria for PE on a validated instrument, the Arabic Index of Premature Ejaculation (AIPE), and excluded were men with erectile dysfunction, low sexual desire, inhibited orgasm, psychiatric or physical illness. Patients were divided into two groups: group 1 (n=77) received sertraline daily for four weeks, while group 2 (n=70) received placebo for four weeks. After a four week washout phase, group 1 received four weeks of placebo and group 2 received four weeks of sertraline. Intravaginal ejaculatory latency time (IVELT) was measured with a stopwatch by the men's partners. Frequency of coitus and IVELT were compared for both groups, and men completed the AIPE at the end of each treatment phase, and monthly during a six month follow-up phase.

Of the original 147 participants, 81% achieved an increase in ejaculatory latency over pretreatment levels with the sertraline treatment. ($p<.001$). The authors note that no participants reported erectile dysfunction, reduced libido or reduced intensity of orgasm. Of 126 men who achieved increased ejaculation latency during sertraline treatment, one hundred were followed for a period of six months after medication discontinuation.

The follow up consisted of once monthly visits during which participants completed the AIPE. Arafa and Shamloul [13] report that of these, 66 experienced relapse of PE within the six month period, evidenced by low AIPE scores. The other 34 men's AIPE scores indicated maintenance of the benefit of ejaculatory delay. Arafa and Shamloul note that the sustained effect of SSRI drugs on ejaculation latency after drug withdrawal is not widely known. They conclude that the present study confirms the usefulness of sertraline in delaying ejaculation, and call for further large cohort studies to "evaluate sertraline's sustained effects on ejaculation latency, specifically after drug discontinuation" [p.537].

Critique

The Safarinejad & Hosseini [12] and Arafa & Shamloul [13] data support the efficacy of SSRIs to delay ejaculation, but are inadequate to establish safety, despite Safarinejad & Hosseini's conclusion that citalopram is "safe and effective" (p. 169) when administered as a chronic, daily, long-term treatment for PE. Given the pervasiveness [18] and randomness [47] with which SSRIs may affect any phase of the sexual response cycle [48] the literature would lead us to expect ejaculation delay to have been accompanied at least in some instances by other unwanted sexual side effects. For example, in a prospective study of SSRI sexual side effects in individuals taking the medications for a variety of approved reasons who had no sexual dysfunctions at baseline, Montejo *et al*. [14] found citalopram or sertraline-treated patients reported, respectively, 62.1% and 54.7% treatment-emergent decreased desire; 63.3% and 56.6% delayed orgasm or ejaculation; and 34.8% and 28.9% erectile dysfunction or decreased vaginal lubrication.

Aspects of the design of the Safarinejad and Hosseini [12] study may have contributed to the absence of findings of concurrent unwanted sexual side effects. Safarinejad and Hosseini note that their assessment instrument, the International Index of Erectile Function (IIEF) is a 15-item, cross-culturally validated, psychometrically sound and sensitive instrument for detecting treatment-related changes in erectile

functioning. The authors used the whole of the 15-item IIEF only at their baseline assessment to screen out men with existing erectile dysfunction. For their assessment of treatment and post-treatment changes, the authors elected to use a subset of six out of the total fifteen IIEF items, comprising a domain of "intercourse satisfaction". Excluded in the ongoing treatment and post treatment assessments were all items concerning erectile functioning. Apparently, participants were expected to self-identify erectile dysfunction, or other sexual adverse events using a diary given to them for recording adverse events. Systematic use of the entire 15 items of the validated instrument for all assessments would have provided a more sensitive method for detecting changes in erectile functioning.

Arafa and Shamloul [13] note that the AIPE is a validated instrument that reliably identifies men with PE and includes assessment of sexual desire, erectile functioning, ejaculation latency, ejaculation control, patient satisfaction, perceived partner satisfaction, and anxiety-depression status related to sexual intercourse. The authors separately present results for each of the seven questions of the AIPE pertaining to the active treatment phase. While the authors note that post-treatment follow-up consisted of monthly administration of the AIPE, results presented are in the form of qualitative comments indicating that AIPE scores were "high" in the group of 34 men who maintained benefits after six months, and "low" in the group of 66 men who relapsed after six months. Changes on the seven domains of sexual functioning as assessed by the AIPE after treatment discontinuation are not presented or discussed. As the study excluded men with sexual problems other than PE, it is of interest to determine whether any participants reported new or different sexual problems post-treatment. The authors note that during active treatment, no erectile dysfunction, reduced libido, or reduced orgasmic intensity were reported. As "reduced intensity of orgasm" is not included among the seven queries in the AIPE, it is not clear how this information was obtained or how systematically.

The results of the Safarinejad and Hosseini [12] and Arafa and Shamloul [13] studies suggest a need for research to clarify the reasons for the persistent sexual benefits after stopping citalopram and sertraline. The placebo and crossover designs establish that the ejaculation delay during active treatment is a medication effect. While a reduction in performance anxiety may potentially contribute to sustained ejaculatory control after cessation of medication [49], Arafa and Shamloul do not present or discuss post-treatment values for the AIEF item related to "anxiety-depression status with intercourse", which might potentially aid in clarifying the contribution of anxiety reduction, if present. It is possible as well, that PE populations may differ in some neurophysiological dimension, as compared to depressed or other clinical populations for whom SSRIs are commonly prescribed. However, post SSRI persistence of biological changes or adaptations can by no means be ruled out [8], are supported by animal studies [50-52], and thus ought to be a cause for concern.

Brief courses of twelve weeks, and of four weeks of medication treatment in the Safarinejad and Hosseini [12] and Arafa and Shamloul [13] studies were sufficient to result in persistence of sexual side effects at very high rates in healthy individuals not suffering from any psychiatric condition. The duration of SSRI treatment in these premature ejaculation studies is considerably shorter than guidelines recommend for approved conditions. It is not known whether the sustained benefits remain stable over a longer period of time than the six months assessed, however it is known that medication-induced sexual side effects may change over the course of time [53, 54]. Montejo and Majadas [53] note that SSRI-related impotence may occur as secondary to disorders of libido, orgasm, or ejaculation that have already lasted for months. Further, they report a positive relationship between the severity of difficulty maintaining sexual arousal and the length of treatment. These findings, of persistent sexual benefits after SSRI treatment discontinuation occurring at high rates in healthy individuals, point to the need to assess the post-treatment duration of the full range of SSRI and SNRI sexual side effects, both positive and deleterious. There seems little reason to assume that SSRI persistent sexual side effects would be confined to those considered desirable by consumers and profitable to industry.

INTERNET-BASED CONSUMER-REPORTS OF PERSISTENT SEXUAL SIDE EFFECTS AFTER DISCONTINUATION OF SSRI/SNRI MEDICATIONS

In a recent issue of *Primary Psychiatr*y, the journal's editor [55], lamented the limits of the post-market pharmacovigilance system, stating that "the time has come for more innovative ways to capture the true incidence of drug safety and tolerability profiles" [p.15]. He calls for careful attention to any real-time, emerging, alternative database of unexpected adverse drug events. The Internet has proven to be a powerful tool for providing just such a database.

Consumer-reported information regarding the persistence of SSRI sexual side effects is available from the SSRIsex Internet community [SSRIsex@yahoogroups.com]. Founded in January of 2005, SSRIsex, a Yahoo discussion group, includes a diverse membership of over fifteen hundred* men and women who report sexual dysfunctions that began as side effects of SSRIs or SNRIs have persisted months and years after stopping the medications. The group's purpose is mutual support, generation of hypotheses about what may have led to the persistent sexual dysfunctions, sharing of information about attempted solutions, and the hope of engaging researchers and professionals in collaborative efforts to understand and address the problem. The group memberships' ongoing moderated conversation now includes over twelve thousand postings. The site also includes a data base where individuals may describe their case history, and numerous voluntary polls related to specific side effects and their duration, specific medications and how long they were taken, as well as remedies attempted along with their results.

Although the group has not been systematically surveyed, it appears on the basis of member postings and informal poll information that any and all sexual side effects that start on the medications may continue after stopping them. Sexual side effects are reported also to sometimes change over time: for example, there are indications that what was initially experienced as a positive ejaculation delay evolved over time into persistent post-medication low libido, impotence, leaking semen, and a precipitous decline in quality of orgasm and genital sensation. Most characteristic of

the condition is reduced genital sensitivity or genital anesthesia, reduced intensity of orgasm or ejaculatory anhedonia, an absence of sexual thoughts or fantasies, erectile problems, and a severely diminished or absent libido.

Information from those who were adolescents at the time of beginning SSRIs/SNRIs indicates that adolescents are by no means immune from sexual side effects, nor from long-lasting post-medication effects. It appears that SSRIs and SNRIs may derail the course of what appears to be on-track, developmentally normative sexual functioning into the same kinds of sexual side effects and persistent difficulties reported by adults. Adolescents in the group seem particularly daunted by the feeling of exclusion from full participation in an important life domain, and the implications of the condition for quality of life, self-concept, intimacy, and future partnership possibilities.

Member reports seem to concur that a shared persistent effect of these medications is a profound diminishment of the physical capacity to experience sexual pleasure. The day to day conversation among this international group of ethnically, gender, sexual orientation and age-diverse membership suggests that the condition of living with post SSRI sexual dysfunction is, for many, a more challenging problem than the condition they originally sought to treat.

* accessed March 2008

CASE REPORTS OF PERSISTENT SEXUAL SIDE EFFECTS AFTER DISCONTINUATION OF SSRI/ SNRI MEDICATIONS

Accumulating case reports of persistent post SSRI sexual dysfunction have appeared in recent literature. All cases involve healthy individuals with no sexual dysfunction reported at baseline, where the treated condition remains in remission, and SSRI or SNRI-emergent sexual dysfunctions continue long after cessation of medication.

Csoka and Shipko [7] describe two men and one woman with normal pre-medication sexual functioning who experienced severely decreased libido, and reduced genital sensitivity and/or reduced orgasmic sensation persisting for years beyond SSRI or SNRI discontinuation. They suggest a number of biological hypotheses to account for the persistent side effects, highlighting the possible role of medication-induced changes in gene expression.

Csoka, Bahrick, and Mehtonen [8] report three more similar cases. The cases of two men are characterized by genital anesthesia, ejaculatory anhedonia, and extremely low libido persisting for several years beyond SSRI or SNRI discontinuation. A third young man was treated at age 18 with four months of fluoxetine for mild anxiety related to a phase of life problem. The new-onset erectile dysfunction he experienced within days of beginning the SSRI has persisted unchanged for eleven years. His libido remains intact. The authors offer further discussion of the possible role of persistent medication-induced epigenetic changes, and propose to call the condition Post SSRI Sexual Dysfunction (PSSD).

Kauffman and Murdock [9] report the case of a 32-year old women with no reported sexual problems at baseline, treated for major depression with citalopram. Due to medication-emergent decreased libido, genital anesthesia, and orgasmic hypo-intensity, she chose to switch after one month to nefazodone, which she continued for 14 months. They report her reduced libido, reduced orgasmic intensity, and genital anesthesia that began with citalopram continued unchanged during nefazodone treatment, and has persisted for the year following completion of all drug therapy. Lubrication and genital engorgement have remained intact.

Bolton, Sareen, and Reiss [6] report a case of genital anesthesia and ejaculatory anhedonia persisting six years beyond cessation of a course of sertraline in an otherwise healthy young man with normal pre-morbid sexual functioning. The authors conclude that the young man's symptoms are more likely a result of a conversion disorder than a lasting medication effect. They base their inferences on the absence of similar reports in the literature and on the indications in the literature that genital anesthesia and ejaculatory anhedonia are rare. The young man was offered an interpretation related to sexual numbing as an unconscious wish to protect himself from rejection, a rejection having been the trigger for the long-resolved depressive symptoms. The patient maintained the conviction that his symptoms were a result of his past medication use, and declined the offer of a course of psychodynamic psychotherapy.

CONCLUSION

The post-market pharmacovigilance system, designed to detect adverse drug events once medications are in widespread use, depends heavily on industry initiative to collect, evaluate, and report data from post marketing studies of their own products [56], creating a major conflict of interest at the heart of our science base. The assumption that sexual side effects will resolve in all cases, the corollary lack of long term follow-up, along with industry's vested interest in outcome make it improbable that the incidence and scope of the problem of persistent SSRI/SNRI sexual side effects will be forthcoming from industry-initiated studies.

Evidence of persistence of SSRI/SNRI sexual side effects also seems unlikely to emerge via voluntary MedWatch reports of health care providers, a system thought to capture only a fraction of adverse drug events [57]. For reasons already discussed, patients as well as health professionals may be skeptical that persistent sexual dysfunctions after medication discontinuation could be medication-related and may misattribute post SSRI sexual dysfunction to psychological causes. A mistaken belief held by many professionals that one needs to be confident of the relationship of the drug to the adverse event in order to report it, along with a common misperception among both health professionals and the public that most adverse drug events are already known at the time of marketing [58], would seem to make the probability especially low that the condition will be reported and identified by this system. While consumers are those directly affected by adverse drug events and therefore have an incentive to report, according to a recent Institute of Medicine report [57] there currently exists no comprehensive method for engaging consumers in the adverse drug event reporting system.

Individuals who have a positive therapeutic response to an SSRI or SNRI, but who also develop sexual dysfunction, are indeed presented with difficult choices in weighing the benefits and risks of continued treatment, particularly when

treatment is intended to be for the long term. By virtue of their typically frequent and regular contact with clients, practicing psychologists, and especially the small number of prescribing psychologists, are in a good position to appreciate and be responsive to the impact of SSRI/SNRI treatment on sexual functioning within the full context of the client's condition and life circumstances [5]. Yet how are the appropriate boundaries among treating professionals best defined? When psychotherapy clients are under informed about medication side effects, who among the treatment providers is responsible for informing clients of risks, and how do psychologists and prescribing professionals most effectively collaborate? How are client welfare and the treatment alliance with the prescribing professional best protected, and under what circumstances would psychologists risk raising client anxiety about the recommendations of their medication-prescribing professional? The reviewed information suggests that for individuals who develop SSRI or SNRI-related sexual dysfunction, there exists an unknown probability that the dysfunctions will continue after medication cessation. Under what circumstances should clients be informed of that risk and by whom?

Psychologists are not negligent as professionals when turning to the formal literature to inform themselves. However when the formal knowledge base is inadequate or inaccurate, treatment providers are all left vulnerable to offering hurtful interpretations or misleading information to clients in spite of their best intentions and best efforts to become well-informed. The inadequacies and inaccuracies in the knowledge base have complex client-welfare and informed consent implications. Informed consent includes an accurate acknowledgement of limits of knowledge. Those limits impose more serious risks than have been realized given the possibility of medication-induced sexual dysfunctions persisting after treatment. Compounding these risks is the near impossibility of gaining a clear picture of how these medications may affect adolescents and children who have no well-established sexual functioning baseline or who are undeveloped sexually.

It is important that research go forward to fill in the gaps in knowledge and that information become available through means that prescribing health professionals find credible. Psychologists should take an active role in this process, seeking to integrate qualitative information from client-reported experiences into the formal knowledge base, and producing original outcome research independent of industry funding and influence.

Absent peer-reviewed research, the convergent information presented here, derived from case reports, incidental research findings, evidence of the persistence of SSRI effects on ejaculation latency, and the experiences of the SSRIsex Internet community membership, currently represents the best available source of information about an SSRI/SNRI-related risk that is of public health significance. The SSRIsex Internet community in particular has credibly gathered, presented and communicated qualitative experiences not captured in the research and not included in the drug's labeling. While each individual report among the Internet group membership is anecdotal, the weight and substance of this collective narrative urgently needs to be reconciled and integrated into the existing knowledge base.

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