

SELECTIVE SEROTONIN REUPTAKE INHIBITORS
AND
SEXUAL FUNCTION

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dedicated to dr. Hugo De Cuyper
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Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs : fluvoxamine -Floxyfral® or Fevarin®, fluoxetine -Prozac®, sertraline -Serlain® or Zoloft®, paroxetine -Seroxat® or Paxil®- and citalopram -Cipramil®-) are potent and competitive inhibitors of the high affinity neuronal re-uptake mechanism for serotonin. These drugs also inhibit the re-uptake of noradrenaline and, generally to a lesser extent, dopamine, at higher concentrations. Paroxetine is the most potent serotonin uptake inhibitor in vitro of the drugs investigated, and citalopram is the most selective inhibitor of serotonin re-uptake, with paroxetine being more selective than fluoxetine, fluvoxamine and sertraline. Of the drugs investigated, only sertraline is a more potent inhibitor of dopamine compared with noradrenaline uptake.

SSRIs are not only as effective as the tricyclic antidepressants in the treatment of major depression but are also effective in the treatment of obsessive-compulsive disorder, panic disorder, eating disorders and premenstrual syndrome (1). Although the latency of onset to therapeutic response seems to be somewhat longer, most psychiatrists consider SSRIs the initial drug of choice in the treatment of depressive disorders. Indeed, these drugs are usually better tolerated since they do not produce muscarinic, histaminic and alpha adrenergic side effects. The most frequently observed side effects of SSRIs are initially gastrointestinal complaints, CNS overstimulation and influences on human sexual behavior. Since adverse effects on sexual behavior impair patient compliance, a more careful description of the published data on SSRIs and sexuality is justified. Moreover, these effects may offer important avenues of understanding of the many unresolved riddles of the neurophysiology of the human sexual response and may even suggest possible new pharmacotherapeutic approaches to the management of sexual dysfunction.

There has, however, been little systematic study of the types of sexual dysfunction produced by these SSRIs ('sexual intercourse is for normal people' -interviewer to a patient-(2)). Available information consists mainly of individual case reports or small series of cases. The information included in these reports is for the present purpose usually incomplete. Authors frequently will mention one type of problem such as decreased libido and fail to comment on other measures. Other important factors such as concomitant medications and especially previous sexual history (before and during the psychiatric disorder) are usually not addressed.

Depressive disorder, obsessive-compulsive disorder, bulimia nervosa and sexual behavior.

It is important to have a closer look at what is known about sexual behavior in patients with the psychiatric disorders for which SSRIs are indicated and commonly used before we review what is presently known about the influence of these drugs on human sexual behavior. The different psychiatric indications for the use of SSRIs indeed present different characteristics in their sexual behavior. Moreover, studies investigating the sexual effects of SSRIs in healthy subjects are unfortunately not available.

Depressed persons are commonly thought to present anhedonia and to have abnormalities in sexual function, including loss of sexual interest, diminished ability to maintain sexual arousal or to achieve orgasm during an episode of major depression, reduced sexual activity, and loss of satisfaction in usual sexual activities (3). However, careful assessment by self report, by behavioral measures and by nocturnal penile tumescence (NPT) demonstrated that the relation between depression and sexual function is more complex. Indeed, diminished sexual interest and satisfaction were demonstrated in men during episodes of major depression, despite normal reported levels of sexual activity, suggesting that loss of sexual interest and of sexual satisfaction are more related to the cognitive set of depression rather than to the actual behavior (4).

Moreover, reductions in NPT time and reduced measures of penile rigidity was shown in approximately 25% to 30% of men in an episode of major depression (5). NPT abnormalities in depressed men further do not reverse when measured in early remission (after cognitive-behavior therapy) and do not correlate with behavioral measures of sexual function in depressed men, suggesting that these alterations in depression may be similar to other persistent electroencephalographic sleep abnormalities in depressed patients in remission, thus being more trait-like than state-like (6).

Similarly, in a mood induction design, it was demonstrated that following depression induction there was a trend toward diminished subjective sexual arousal in the early portion of erotic exposure, and achievement of maximum subjective arousal was delayed; however, penile tumescence was unaffected. This experiment again suggests a divergence between subjective sexual and somatic arousal (7).

The notion that sexual conflict is a causal factor in the development of obsessive compulsive disorder has been a recurrent theme in the literature. One characteristic of obsessive compulsives is the need for control and object mastery; these needs are alleged to be defense mechanisms, employed as a means of coping with repressed impulses of hostility, violence, and sexuality, which directly result from fixation in the anal stage of development (8,9). The studies investigating sexual behavior in obsessive compulsives are methodologically weak and most often based only on self-report measures. Since they only question the conscious level of sexual function, attitude and history, it is quite obvious that they never can directly confirm or falsify the psychoanalytic hypothesis. Some important findings should however be mentioned in the context of the present article: a high proportion of obsessive compulsives (40-50%) are celibate; about one-third of patients report sexual obsessions (about intercourse, about homosexuality, about masturbation and regarding bodily secretions)(10). Other findings, however, showed that obsessive compulsive individuals cannot be distinguished from either depressive or panic disordered groups by a particular sexual history, present life, sexual satisfaction and marital adjustment (11).

Patients with bulimia nervosa are known to indulge not only in eating binges but also in increased smoking, drinking and sexual behavior (12). They are usually 'hungry' for food but also for love and sexual experiences. More than 20% of patients with bulimia nervosa present borderline personality. And in an aspecific borderline sample, it was shown that about 50% of the women reported a childhood history of physical or sexual abuse; borderline women were also found to have significantly higher sexual assertiveness, greater erotophilic attitudes, and higher sexual esteem; but, despite these findings, borderline patients evidence significantly greater sexual preoccupation, sexual depression, and sexual dissatisfaction (13).

**Effects of antidepressant medication on sexual function :
SSRIs versus other antidepressant drugs.**

Sexual dysfunctions appear to be frequently occurring adverse events during treatment with antidepressants. Due to methodological reasons, a reliable estimation of the frequency of such events is currently not yet possible. There is evidence, that antidepressants could be differentiated with respect to their potency and specificity for disturbances of certain sexual subfunctions according to their pharmacological profile.

Sexual side-effects seem to be more frequent in patients taking SSRIs than in patients taking tricyclic or tetracyclic antidepressants (10 to 30% versus 5 to 10%) (14). Sexual side effects reported with the use of antidepressants include loss of libido, erectile dysfunction, impaired arousal and lubrication, delayed or painful ejaculation or delayed orgasm (15). Orgasm and ejaculation are often impaired to a greater extent than erection. Adverse sexual function changes secondary to antidepressant medication occur frequently in both men and women, although men report a higher incidence (16).

It should be remembered that painful ejaculation (which is different from prolonged erections or priapism) is also an underreported adverse sexual side effect of tricyclic antidepressants like clomipramine or imipramine (real prevalence about 18% in males) (17,18). Patients describe painful ejaculation as a painful burning sensation accompanying ejaculation and interfering with the pleasure of intercourse.

With SSRIs in particular impaired functions of orgasm and ejaculation can be observed. No deteriorations are reported for bupropion (a new nontricyclic antidepressant with a relatively simple amino ketone chemical structure) and an improvement of sexual dysfunctions within the course of treatment for moclobemide (a new Reversible Inhibitor of Monoamine oxidase-A (RIMA)) (19,20). Viloxazine (an atypical antidepressant) seems also to be free of sexual side effects and trazodone appears to possess marked stimulating effects on libido and erectile functions although a negative effect on ejaculation and orgasm was also reported (21-25).

Effects of SSRIs on human sexuality

The majority of the reports on sexual dysfunction during treatment are based on anecdotal or impressionistic claims and individual case reports. Neither drug studies nor postmarketing surveillance has provided adequate information about the incidence or type of sexual dysfunction produced by SSRIs. 'Medical doctors are not experts on sex'. Clinical psychiatrists (as well as gynecologists, andrologists or urologists) are usually afraid of 'penetrating' sexual intimacy.

Sexual side effects occur in 10-30% of men or women taking SSRIs. The most frequently reported sexual side effects of SSRIs are delayed ejaculation and anejaculation, delayed orgasm and anorgasmia. This was reported in men and women, taking SSRIs as well for the treatment of depression, panic attacks, obsessive-compulsive disorder or bulimia (26,27). It was shown that after reducing the dose of fluoxetine (which helps in about 50% of patients) or after discontinuation of the drug, patients take several weeks before they reach their pre-treatment level of sexual functioning (28,29).

Ejaculatory difficulty, anorgasmia and loss of libido were also described in the use of paroxetine (30-32) and sertraline (33,34).

Penile anesthesia has been described with 20 mg/day of fluoxetine and this lead to ejaculatory difficulties after 3 months of treatment, suggesting a spectrum of side effects from penile anesthesia to anorgasmia (35,36). Vaginal anesthesia was also reported in a women over the course of 1 week of fluoxetine 20mg/day noticing decreased sensation in het vagina and vulva which progressed to total anesthesia by week 2; after discontinuation of fluoxetine, genital sensation only gradually returned to normal over a 4-week period (37).

But the sexual side effects of the SSRIs may be more variable than previously thought. Animal models showing paradoxical or opposing responses to serotonin-enhancing agents may apply to human sexual functioning as well. Indeed, several cases of return of sexual potency without priapism in elderly impotent men taking fluoxetine were reported (38). The details of these cases suggest that the return of potency was unrelated to remission of depressive or obsessive-compulsive symptoms. Moreover, more than 30 cases of prolonged erections associated with fluoxetine have been reported to the drug's manufacturer (Dista Products Company, Indianapolis, Ind.). There were also repeated observations of yawning, clitoral engorgement and orgasm with fluoxetine (which was also described for clomipramine) administration : the yawning was in the absence of drowsiness and the multiple orgasms associated with clitoral engorgement were in the absence of voluntary sexual stimulation (39,40). These symptoms occurred after only a few days of fluoxetine intake; both the yawning and the sexual feelings disappeared within 1 day of dosage decrease. It was suggested that patients with organic brain disease may be at higher risk for the occurrence of short episodes of sexual excitement with the use of fluoxetine (41).

The mechanisms for these variable sexual side effects of SSRIs are largely unknown and thus speculative. The apparent paradox of serotonergic enhancement associated with either increased or decreased sexual functioning has correlates in sleep and in animal models of sexual and feeding behaviors (42-44). Serotonergic systems have been implicated in the regulation of the sexual response, although data are conflicting as to whether the role of serotonin is primarily inhibitory, excitatory, or possibly mixed. Mechanisms proposed to explain these contradictory phenomena include antagonistic serotonin receptor subtypes, partial agonist/antagonist neurotransmitters, or receptor down-regulation leading to altered serotonin release (44). Increased amounts of serotonin may be working directly on central, spinal, or peripheral receptors or a combination of these receptors to influence the sexual response. More important, perhaps, is the possible indirect role serotonin may play on central, spinal, or peripheral mechanisms. A functional connection between serotonin and noradrenergic neurons has been implicated in several proposed mechanisms of antidepressant action. Since the adrenergic system is implicated, at least in part, in the excitatory mechanism of orgasm, perhaps serotonin is merely playing an inhibitory role on the noradrenergic input or in the interaction of other neurotransmitter systems (45).

The occurrence of yawning, clitoral engorgement and spontaneous orgasms associated with fluoxetine administration has been explained by a reciprocal balance of serotonergic activation, dopaminergic inhibition and cholinergic activation although an opiate withdrawal phenomenon was also suggested (39,46).

Management of sexual side effects of SSRIs

Dosage decrease or discontinuation of the SSRI usually result in disappearance of the sexual side effects. However, these sexual side effects also seem to be responsive to several treatments.

Cyproheptadine hydrochloride (Periactin®), an antihistaminic and antiserotonergic drug, has been reported to reverse anorgasmia caused by both tricyclic antidepressants and monoamine oxidase inhibitors (47-49). It has been proposed to administer 4 to 12 mg ninety minutes before anticipated sexual activity, but drowsiness as a side effect of cyproheptadine can occur at high doses (50). Anorgasmia or delayed ejaculation as a side effect of paroxetine and fluoxetine have been shown to be reversed by cyproheptadine (51-54) in depressive as well as in bulimic patients. Moreover, fluoxetine-induced yawning has also been shown to be reversed by cyproheptadine, suggesting that cyproheptadine is able to counter the adverse effects of fluoxetine by antagonizing serotonin's effects on the dopaminergic pathways (55). However, in some of these patients, the administration of the antiserotonergic drug resulted in a reversal of the antidepressant or antibulimic activity of fluoxetine (53-54), which casts doubt on the clinical usefulness of cyproheptadine for the treatment of SSRI induced sexual side effects.

Yohimbine (Yohimbine®), a presynaptic α 2-adrenergic receptor blocker may be increasing inflow and decreasing outflow of blood from erectile tissue while also enhancing libido from cortical activation, has also been suggested to have a potential utility in reversing fluoxetine-induced sexual dysfunction (56,57). Patients with either obsessive-compulsive disorder, trichotillomania, anxiety or affective disorders who suffered sexual side effects after treatment with SSRIs have been treated successfully with yohimbine: most patients reported improvement in sexual function, although several patients reported side effects (mild headache, nausea, anxiety, excessive sweating, insomnia and urinary frequency) which led to the discontinuation of yohimbine in some cases. It has been suggested that patients need individualized optimal doses (2-15 mg/day). Since yohimbine has a relatively short half-life, it has been proposed to take the tablets 90 minutes before intercourse. The predominantly serotonergic activity of fluoxetine does not appear to contraindicate the concurrent use of yohimbine (potentially adverse cholinergic and adrenergic interactive effects are possible with the tricyclic antidepressants) (58).

Amantadine (Amantan®, Mantadix®), a mild dopamine agonist, can be added to the treatment armamentarium for delayed orgasm and anorgasmia induced by fluoxetine (59). It has been proposed to prescribe 100 mg twice daily. Animal studies indeed suggest that serotonin inhibits while dopamine facilitates ejaculation. It should be noted that fluoxetine indeed has been reported to induce side effects due to interference with dopamine receptors (60,61).

The possible benefits of the sexual side-effects from SSRIs.

Sexual side effects from SSRIs seem to have been underrecognized during the past decade. Indeed, spontaneous reporting as well as direct questioning are open to many biases. Both are dependent upon the relationship between the patient and the doctor. Women may be more reluctant to discuss sexual problems than men, at least when being treated by a male physician; physicians may be less inclined to ask elderly patients about their sexual function and may even fail to report sexual side effects (62). Moreover, if about 10% of men in the general population (and more than 20% of the younger men in a sexual clinic population suffer from premature ejaculation (insufficient control over ejaculation), a sexual side effect like delayed ejaculation is very likely to be underreported since this side effect can be experienced as beneficial (63,64). It is indeed well known that there is a bias towards reporting only negative effects (62).

There have indeed been some reports of a beneficial effect from SSRIs achieved in patients with premature ejaculation (65-67). Clomipramine (Anafranil®, 25 mg ingested orally before bedtime) which has also some effects on serotonin reuptake blockade has indeed also been suggested for the treatment of premature ejaculation although its effectiveness could also be due to its ability to inhibit adrenergic receptors of the peripheral sympathetic system (68,69). Some authors proposed that at least a subcategory of premature ejaculators possess a hypersensitive sympathetic nervous system preventing them from differentiating between ejaculation and its inevitability and/or once the sympathetic nervous system is triggered, it has to discharge (68,70). Caution however has to be exercised in extrapolating from single case reports and again further research is needed.

Although the DSM-IV classifies paraphilias on axis I as sexual disorders, they are also explicitly recognized on axis I as impulse control disorders in the section "Disorders of Impulse Control Not Elsewhere Classified" (71). The paraphilias (including voyeurism and exhibitionism, fetishism, pedophilia, frotteurism, zoophilia, sexual masochism and sexual sadism) have as an essential feature recurrent, persistent fantasies about deviant sex. Individuals experience erotic feelings or impulses, perceived as noxious when frustrated. There is a sense of mounting tension prior to committing the act, which is often carried out in a stereotyped fashion. While there may be gratification or release at the time, often guilt and remorse follow.

Phenomenological similarities between the paraphilias and the obsessive-compulsive disorders (OCDs) are apparent and reflected in the many parallels in the diagnostic criteria (72). Recently there has been increased recognition that the OCDs and others, including kleptomania, trichotillomania, compulsive gambling, compulsive sexual behaviors, eating disorders, and addictive disorders, may be related (73). Anyhow, there is no consensus as to whether compulsive sexual behavior is best described as a 'psychosexual, obsessive-compulsive personality, impulse or addictive disorder' (74). Those working within a cognitive behavioral model have long recognized the importance of treating the dual nature of the paraphilias, and therapy is directed both at altering the specific deviant drive and improving impulse control (75). In contrast, the physical treatments of the paraphilias have derived from a model emphasizing the need to reduce the strength of the sex drive (orchidectomy, stereotaxic surgery, antiandrogenic therapy) or from a model emphasizing the need to improve impulse control (dopamine antagonists, SSRIs).

Cases of fluoxetine treatment (10 to 60 mg/day, the dose most frequently reported to be successful seems 40 mg/day) of exhibitionism, fetishism, voyeurism/frotteurism, pedophilia, and of nonparaphilic sexual addictions (compulsive masturbation, ego-dystonic promiscuity, dependence on anonymous forms of sexual outlet -pornography, phone sex-) have been reported (76-82). Successful treatment of exhibitionism and fetishism was also reported with fluvoxamine and sertraline (83,84). It is still not yet clear whether it are mainly the sexual obsessions or compulsions or the paraphilias themselves which are responsive to SSRI treatment. It is still not yet clear whether, in the case of paraphilia, SSRIs inhibit only the deviant sexual impulses or sexual behavior in general. Moreover, a consensus on the exact definitions of sexual obsessions, sexual compulsivity, sexual dependency, sexual addiction and sexual impulse control disorder still has to be found (85,86).

Conclusions.

The influence of the SSRIs on human sexual behavior is insufficiently known and is more complex than initially thought. There seem to be negative (delayed orgasm or delayed ejaculation, decreased libido, priapism and spontaneous orgasms) as well as positive (restoration of erectile function) sexual side effects. However, the negative sexual side effects can probably be used successfully in specific clinical situations like premature ejaculation or paraphilias and sexual addictions.

Millions of people take SSRIs for several psychiatric disorders and 10 to 30 % of them present sexual side effects. The present review is merely an invitation to a more careful 'listening to' people taking SSRIs and to a more careful research on the sexual side effects of SSRIs. Indeed, side effects are frequently a major hinderance to compliance with antidepressant treatment. Therefore, we hope that the defence mechanisms like 'sexual intercourse is only for "normal" people' belong to the long-ago also in psychiatric practices.

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Discussion - SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEXUAL
FUNCTION

R.T. Segraves

At this point I am aware of four double blind studies with either chlomipramine, sertraline and paroxetine for treatment of premature ejaculation, excluding the one you have started, so I think there is pretty good controlled evidence of the efficacy of these drugs. It was earlier discussed with chlomipramine whether this was a change in time perception or a real change. Steve Levine in Cleveland actually used a stopwatch and had people click the stopwatch before intromission and then click off after ejaculation. So I think this is pretty well established that these drugs cause ejaculatory delay.