1.1. SSRIs and persistent sexual dysfunction

Introduction

The serotonin reuptake inhibitors (SSRIs) are indicated for *the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder* [1-7]. SSRIs available on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Fevarin®), paroxetine (Seroxat®), and sertraline (Zoloft®). Venlafaxine (Efexor®) in a dosage less than 150 mg is also considered an SSRI [8].

Sexual dysfunction is a known side effect of SSRI treatment. SSRIs are associated with decreased libido, erectile dysfunction, ejaculatory disturbances, delayed orgasm and anorgasmia [1-7]. These dysfunctions typically endure for as long as the medication is taken and it has generally been assumed that these effects would resolve upon discontinuation of treatment. However, there is emerging evidence that in some individuals sexual dysfunction is persistent after cessation of SSRIs.

Reports

On February 22nd 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained 19 reports of persistent sexual dysfunction in patients who had used SSRIs in the past.

Most cases were reported by consumers (n=15). The other reports were from general practitioners, a pharmacist and a pharmaceutical company. Reports were received for various SSRIs: paroxetine (n=5), sertraline (n=4), venlafaxine (n=4), citalopram (n=4), fluoxetine (n=2), fluvoxamine (n=1) and escitalopram (n=1).

Reported adverse drug reactions were delayed ejaculation (n=2), ejaculation disorder (n=2), decreased libido (n=5), impotence (n=1), sexual dysfunction NOS (n=7), erectile dysfunction (n=3) and female orgasmic disorder (n=1). Thirteen reports concerned males and six reports females. The median age was 30 years and ranged from 20 to 59 years.

Latencies ranged from days to years, however in most cases patients experienced sexual dysfunction after days of SSRI use. Duration of treatment with SSRIs was a few months to two years in most cases (range 9 days – 10 years). SSRIs were withdrawn in all patients. The time since withdrawal of the SSRI and still having sexual dysfunction varied from two months to two years.

In most cases no concomitant medication was reported (n=16). In the remaining cases (n=3) reported co-medication consisted of zolpidem, oxazepam, lorazepam, sildenafil and levothyroxine. The one patient that used sildenafil (for over five years) reported delayed ejaculation problems days after start of sertraline.

Other sources of information

SmPC

The Dutch SmPCs of the various SSRIs mention sexual dysfunction (loss of libido, erectile dysfunction, ejaculation disorder, abnormal orgasm and anorgasmia). The various Dutch SmPCs make no mention of the possible persistent nature after drug cessation of these sexual dysfunctions [1-7].

The US SmPC of fluoxetine mentions that symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment [9]. The US SmPCs of the other SSRIs do not mention the persistent nature of sexual dysfunction [10-15].

Literature

In an observational study evaluating whether drug holidays would improve sexual functioning in recovered depressed patients with SSRI-induced sexual dysfunction (n=30) it was shown that fluoxetine was the only SSRI for which improvement of sexual functioning did not occur after brief cessation of administration [16].

Csoka *et al.* [17] describe three cases of persistent sexual dysfunction after discontinuation of SSRIs. A 29-year-old male with apparently permanent erectile dysfunction after taking fluoxetine 20 mg once daily for a 4-month period, a 44-year-old male with persistent loss of libido, genital anesthesia and erectile dysfunction after taking 20-mg once daily citalopram for 18 months and a 28-year-old male with persistent loss of libido and genital anesthesia since taking several different SSRIs over a 2-year period. No psychological issues related to sexuality were found in any of the three cases and all common causes of sexual dysfunction such as decreased testosterone, increased prolactin or diabetes were ruled out.

Csoka and Shipko [18] also describe three other cases of persistent sexual dysfunction after SSRI discontinuation. A 24-year-old male with reduced libido and severe genital insensitivity after two years use of citalopram 20 mg once daily, a 27-year-old female who used 20 mg fluoxetine once daily experienced total loss of libido and a 30-year-old male who experienced a severe drop in sexual desire, erectile dysfunction and genital numbness after using 50 mg sertraline once daily.

Kaufmann and Murdock [19] describe a 32-year-old female with major depression who was treated with citalopram but switched to nefazodone after 4 weeks of therapy due to genital anesthesia and orgasmic dysfunction. These symptoms continued during nefazodone therapy and have persisted for over a year since termination of the antidepressant treatment. Her depression remains in full remission.

Databases

It is not possible to calculate a Reporting Odds Ratio for persistent sexual dysfunction since only the specific cases in which the patients report that they have not recovered after discontinuation of treatment must be taken into account.

Prescription data

The number of patients using SSRIs in the Netherlands is shown in Table 1 [20].

Table 1. Number of patients using SSRIs in the Netherlands between 2006 and 2010.

Drug	2006	2007	2008	2009	2010
Citalopram	125,600	132,700	135,430	137,880	142,840
Escitalopram	19,384	27,626	32,351	37,777	45,461
Fluoxetine	63,670	59,351	57,341	54,346	53,311
Fluvoxamine	31,675	28,304	26,415	24,654	24,236

Drug	2006	2007	2008	2009	2010
Paroxetine	267,820	245,620	230,470	214,660	205,700
Sertraline	56,385	53,600	51,810	52,477	55,899
Venlafaxine	116,520	121,840	121,740	115,080	113,930

Mechanism

It is currently not known what causes the sexual adverse effects of SSRIs to persist after discontinuation. Sexual response is complex and involves dopaminergic, adrenergic, muscarinic, and serotonergic neurotransmitters. Various mechanistic hypotheses including persistent endocrine and epigenetic gene expression alterations have been proposed. The numerous biochemical and neurochemical changes that occur during SSRI use account for their sexual adverse drug reaction. These abnormal gene expression profiles return to normal upon medication withdrawal. Although transporter and receptor densities and cerebral gene expression probably normalise in most patients, it is possible that there are significant delays in some patients. Furthermore, serotonergic receptors are involved in the negative feedback regulation of the hypothalamic-pituitary-testicular axis. Elevated serotonin in the hypothalamus could result in down-regulation of this axis, creating lowered free testosterone levels. These changes may not fully normalise in some patients [18].

Discussion and conclusion

It has previously been assumed that sexual adverse drug reactions always resolve shortly after SSRI discontinuation [19]. Emerging evidence, however, suggests that in some individuals, sexual dysfunction may persist indefinitely. Lareb received 19 reports of persistent sexual dysfunction after SSRI use. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, these reports suggest that they may also be a consequence of SSRI treatment. The symptoms occurred soon after start of the medication and some patients reported explicitly that relational problems or sexual function disorders were not present before start of the SSRI. Some patients also reported that the depression remained in full remission, but the sexual function disorder persisted.
Erectile function is known to decrease with age, but these reports concerned males with a median age of 30 years. Diabetes, vascular disease and neurologic disease can affect erectile function [21]. In the cases reported to Lareb no concomitant medication was used that indicated these types of comorbidities. There was one patient who used sildenafil for five years but he reported delayed ejaculation problems days after start of sertraline.
In the literature several case reports of persistent sexual dysfunction after discontinuation of SSRI treatment have been described and the US SmPC of fluoxetine already mentions that symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment [9,17-19].
The persistent nature of the sexual dysfunction associated with SSRI treatment described in the literature as well as the reported cases by Lareb support further investigation.

- Signal of SSRIs and Post SSRI Sexual Dysfunction
- Further investigation of the information of the marketing authorisation holders is advisable

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This signal has been raised on October 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).