Lareb
Nederlands Bijwerkingen Centrum
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SSRIs and flushing, hot flushes and blushing

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 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].
Flushing may be defined as a sensation of warmth accompanied by visible reddening of the skin. Flushing is usually most prominent in the classic “blush area”, which includes the face, neck, upper portion of the chest and upper limbs [9]. More or less similar or closely related reactions are blushing and hot flushes. Blushing is defined as involuntary reddening, especially of the face, associated with feelings of embarrassment, confusion or shame [10]. Hot flushes are described as a sudden, temporary sensation of heat predominantly experienced by some women during menopause [10].
The SmPC of sertraline mentions hot flushes and flushing as possible adverse drug reactions, the SmPC of venlafaxine mentions hot flushes and blushing. The SmPCs of the other SSRIs do not mention flushing, blushing, or hot flushes [1-7].

Reports

On January 14 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained 10 reports of flushing and 24 reports of hot flushes in association with SSRIs and venlafaxine.
Of the reports about hot flushes 7 reports were about venlafaxine, 6 about paroxetine, 3 about citalopram, 4 about fluoxetine, 3 about fluvoxamine and 1 about sertraline.
Of the reports about flushing, 4 were about venlafaxine, 3 about citalopram, 2 about paroxetine and 1 about fluoxetine.
Six of the reports were submitted by the marketing authorization holder. There were 30 female patients and 4 male patients. The patient’s age was known in 33 cases; mean age was 45.8 years, the median 42.0 years (SD 15.9 years, minimum 18 years, maximum 85 years).
The latency was reported in 27 cases; mean latency was 169 days, the median 3.5 days (SD 713.7 days, minimum 2 hours, maximum 10 years). In 2 cases the adverse reaction appeared after withdrawal of the drug. Latency was unknown in 2 cases.
In 16 cases the drug was withdrawn, the outcome was reported as recovered/recovering in 8 of these cases. There was a dose reduction three times, one of the patients recovered. In 12 cases the dose was not changed, one of the patients however did recover. In 2 cases the action with the drug is unknown.
In 5 cases the outcome was reported as not recovered. The outcome of the other cases is unknown.
In 2 cases the reporter mentions the patient experienced the same adverse drug reaction during earlier use of the drug. In one case the patient experienced hot flushes in the past while using escitalopram and experienced the same events now while using fluoxetine.

A few index cases will be described below.

Patient A was a female over 70 years, who developed hot flushes one day after start of fluoxetine for a depressive episode. She also used lorazepam, promethazine syrup, furosemide and captopril. Fluoxetine was withdrawn, the outcome is unknown. The patient experienced the same reaction in the past after taking fluoxetine.

Patient B is a female between 41 and 50 years with flushing one day after start of fluoxetine for a panic disorder. Fluoxetine was withdrawn and the patient recovered. No comedication was reported.

Patient C is a male between 51 and 60 years, who used amlodipine, losartan, diclofenac/misprostol and oxazepam. Five days after start of paroxetine for a depression, he developed hot flushes that recovered after withdrawal of the drug.

Patient D is a female between 11 and 20 years, who experienced hot flushes 6 weeks after start of fluoxetine for a depression. She also used quetiapine. The dose of fluoxetine was not changed and the outcome is unknown. The patient experienced the same adverse drug reaction with escitalopram in the past.

Other sources of information

SmPC

The Dutch SmPC of sertraline mentions hot flushes and flushing. The SmPC of venlafaxine mentions hot flushes and blushing. The SmPCs of the other SSRIs mentions neither of these symptoms [1-7]. However, in the American SmPC of paroxetine flushing is described [11].

Literature

(Facial) flushing as part of a serotonin syndrome was associated with SSRIs and venlafaxine in case reports [12-15].
On the contrary, several review articles describe the use of SSRIs and SNRIs in the treatment of hot flushes [16-18].

Databases

On January 14 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained 17 cases of hot flush and 6 cases of flushing in the association with SSRIs and 7 cases of hot flush and 4 cases of flushing in the association with venlafaxine. For hot flush, the ROR was neither statistically disproportional for individual SSRIs, nor for SSRIs as a group (ROR=1.4, 95% CI: 0,9 – 2.3). The ROR was statistically disproportional for hot flush and venlafaxine (ROR= 2.1, 95% CI: 1.0 – 4.4). For flushing, the ROR was not statistically disproportional for SSRIs or venlafaxine (Table 1).

Table 1. Reporting odds ratios of SSRIs and venlafaxine and hot flush and flushing in the Lareb database.

Drug and ADR	Number of reports	ROR (95% CI)
SSRIs and hot flush	17	1.4 (0.9-2.3)
SSRIs and flushing	6	0.4 (0.2-0.8)
Venlafaxine and hot flush	7	2.1 (1.0-4.4)
Venlafaxine and flushing	4	0.9 (0.3-2.4)

On January 28 2011, the database of the World Health Organization contained 275 cases of the Preferred Term “hot flush” in association with SSRIs and 556

cases of flushing. The reporting odds ratio for these associations was not statistically disproportional (Table 2). For hot flush and venlafaxine (88 cases), the ROR was statistically disproportional (ROR=2.28, 95% CI 1.85 – 2.81). The ROR for flushing and venlafaxine (127 cases) was not statistically disproportional.

Table 2. Reporting odds ratios of SSRIs and venlafaxine and hot flush and flushing in the WHO Pharmacovigilance database.

Drug and ADR	Number of reports	ROR (95% CI)
SSRIs and hot flush	275	1.10 (0.98-1.24)
SSRIs and flushing	556	0.38 (0.35-0.41)
Venlafaxine and hot flush	88	2.28 (1.85-2.81)
Venlafaxine and flushing	127	0.55 (0.46-0.66)

Prescription data

The number of patients using SSRIs and venlafaxine is shown in Table 3 [19].

Table 3. Number of SSRI/venlafaxine users in the Netherlands between 2005 and 2009.

Drug	2005	2006	2007	2008	2009
Citalopram	23,292,300	22,262,800	23,798,300	13,166,800	8,961,800
Escitalopram	1,449,400	3,421,000	5,803,700	7,189,600	8,180,700
Fluoxetine	9,323,800	8,360,300	8,347,500	4,688,800	3,089,900
Fluvoxamine	7,277,600	6,493,700	5,890,400	3,425,000	2,059,500
Paroxetine	57,825,100	47,873,800	42,495,800	23,238,400	13,291,000
Sertraline	16,616,500	11,192,600	11,442,900	5,838,800	3,810,500
Venlafaxine	32,797,400	33,561,900	38,500,500	40,939,100	15,539,000

Mechanism

Evidence from animal studies suggests that serotonin (5-HT) plays an important role in thermoregulation and that the temperature increases associated with hot flushes and flushing could be linked to an overload of serotonin receptor sites in the hypothalamus. Two 5-HT receptor subtypes, 5-HT1a and 5-HT2a, are believed to be most closely associated with temperature control in mammals. These receptors appear to have opposite effects on temperature regulation, with 5-HT2a mediating hyperthermic effects and 5-HT1a mediating hypothermic effects. Results from studies in rodents and human beings suggest that a balance between the 5-HT1a and 5-HT2a receptors might be important for optimum thermoregulation in mammals [20,21]. Dysbalans between the 5-HT1a and 5-HT2a receptors could lead to hypothermic effects like hot flushing or flushing or hypothermic effects like rigor/chills. In the Lareb database both hypothermic and hypothermic effects have been reported for the SSRIs.
A recent hypothesis is that oestrogen withdrawal (like in menopause) could be associated with a decline in circulating serotonin, thus increasing sensitivity of the hypothalamic 5-HT2a receptor [20]. By giving an SSRI the serotonin concentration rises and the 5-HT2a receptor is stimulated. As a result, there is a change in the thermoregulatory set-point and a hot flush sensation [20].

Conclusion

The Lareb database contains several reports of hot flush and flushing in association with SSRIs and venlafaxine. The reports mainly concern females and the mean age of 45.8 years suggests menopause could be an important confounder. There are however also several cases of male patients and younger and older females. In two out of seven Dutch SmPCs of SSRIs and venlafaxine flushing or comparable descriptions are mentioned. Although case reports only mention flushing as part of a serotonin syndrome and review articles describe the use of SSRIs and SNRIs in the treatment of hot flushes, there is a possible mechanism that would explain the appearance of flushing in the use of SSRIs and venlafaxine.

- Possible new signal of flushing/hot flushes associated with the use of SSRIs and venlafaxine.

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