SSRIs and aggression

Introduction

Selective serotonin reuptake inhibitors (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.
SSRIs are indicated for *the treatment of major depressive disorder*. Besides depression some SSRIs are indicated for *obsessive compulsive disorder* (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) *panic- and/or anxiety disorder* (escitalopram, paroxetine, sertraline, venlafaxine) and *posttraumatic stress disorder* (paroxetine, sertraline) [1-7]. The efficacy of SSRIs is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin [3]. The first SSRI to be granted marketing authorization in the Netherlands was fluvoxamine in 1985 [4].

Aggression is defined as goal-directed motor behaviour that is intended to harm or injure another person or object [8]. The pathogenesis of violent behaviour is not well understood. A wide range of factors may play a role, including the environment, a patient's social and medical history, interpersonal relations, genetics, neurochemistry and endocrine function, and substance abuse. Known psychiatric illness is a risk factor for violent behaviour, with schizophrenia (paranoid and nonparanoid), personality disorders, mania and psychotic depression most often associated with violence. Psychosis, delirium or dementia may lead to violent behaviour [9].

In July 2009 Lareb described the association between aggression and the use of SSRIs in a quarterly report. The current observation is an update of this association.

Reports

Between November 10th 1994 and January 9th 2014, the Netherlands Pharmacovigilance Centre Lareb received 78 reports of aggression associated with the use of SSRIs (paroxetine (n=26), venlafaxine (n=19, dose range 75-225 mg/day), fluoxetine (n=14), citalopram (n=13), fluvoxamine (n=7), escitalopram (n=6) and sertraline (n=3)). Some patients reported aggression on more than one SSRI. In general, 1 to 8 reports per year were received, except for 2010 when 26 reports were received. This high number in 2010 is probably due to media attention.
Forty-three reports were serious and 35 reports were non-serious. Most reports were reported by consumers (n=35). The other reports were received from marketing authorisation holders (n=17; of which consumers (n=13), specialist doctors (n=3) and literature report (n=1)), specialist doctors (n=10), general practitioners (n=5), (hospital) pharmacists (n=5), reporter unknown (n=3), literature reports (n=2) and a specialist nurse (n=1). Forty-five reports concerned men and 33 reports concerned women. Most patients used the SSRI for depression (n=49). Other reported indications were posttraumatic stress disorder (n=3), panic- or anxiety disorder (n=3), borderline personality (n=2), burn-out (n=2), stress (n=1), neuralgia (n=1), psychiatric disorder NOS (n=1) and unknown (n=16). The median age was 37 years and ranged from 10 to 76 years. Time to onset varied from one hour to 10 years (median latency 14 days). One patient reported aggression after

withdrawal of paroxetine due to withdrawal symptoms (insomnia). Twenty-nine patients recovered or were recovering after stopping treatment with the SSRI. Two patients discontinued the use of the SSRI but had not recovered at the time of reporting. Of the eight patients who did not change the medication three recovered and five did not recover. Of the seven patients who reduced the dose, six recovered and one did not recover and of the three patients who increased the dose, one recovered and two did not recover. Three patients died; two committed suicide and of the other patient the cause of death is unknown. Twenty-six patients did not report the action with the drug or the outcome.
In 24 reports the SSRI was reported as the only suspect drug and no other drugs or causes were reported. Possible causes reported by others were already being known with aggression, extreme lack of sleep, relational problems, excessive use of alcohol, smoking cessation, stress, multiple CVA's/TIA's and problems at work. One patient reported aggression only in combination with coffee. Without coffee he experienced no problems. Two patients reported aggression when using a generic SSRI and they did not experience problems when using the brand product. The aggressiveness can be severe.

Other sources of information

SmPC

Aggression is mentioned in the SmPC of citalopram, escitalopram, sertraline and venlafaxine [1,2,6,7]. The SmPC's of fluoxetine, fluvoxamine and paroxetine mention aggression only in children and adolescents younger than 18 years old [3-5].

Literature

Although several studies describe a role for serotonin in aggression [10,11], there is no consensus in the literature about the effect that the use of SSRIs may have on aggression. A review article from Walsh and Dinan [12] reviewed all published papers on Medline and other databases linking serotonin, SSRIs and aggression. They conclude that there is no convincing evidence to link SSRIs causally to violence and suicide. A small proportion of patients treated with SSRIs may become akathisic and others may show increases in anxiety in the initial phase of treatment but no increased susceptibility to aggression nor suicidality can be connected with the SSRIs. In fact, SSRI treatment may reduce aggression, probably due to positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour directed towards oneself or others.
However, a review and analysis by Breggin [13] states that evidence from many sources (clinical reports, controlled clinical trials and epidemiological studies) confirms that SSRIs commonly cause or exacerbate a wide range of abnormal mental and behavioural conditions. This can result in suicidality, violence and other forms of extreme abnormal behaviour.

Databases

On January 9th 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained 78 reports of aggression associated with the use of SSRIs. Because one report can contain multiple suspect drugs, the total number of SSRIs associated with aggression is 88.

Table 1. Reports of aggression for the SSRIs in the Lareb, WHO and Eudravigilance database.

Database	Drug	Number of reports	ROR (95% CI)
Lareb	Citalopram	13	4.2 (2.4-7.3)
	Escitalopram	6	6.6 (2.9-14.9)
	Fluoxetine	14	6.4 (3.7-10.9)
	Fluvoxamine	7	4.4 (2.1-9.3)
	Paroxetine	26	3.7 (2.5-5.5)
	Sertraline	3	1.9 (0.6-5.8)
	Venlafaxine	19	4.2 (2.6-6.6)
	Total	**88**	**4.7 (3.7-5.9)**
WHO	Citalopram	272	3.4 (3.0-3.9)
	Escitalopram	196	4.6 (4.0-5.3)
	Fluoxetine	1226	6.1 (5.7-6.4)
	Fluvoxamine	105	3.6 (3.0-4.4)
	Paroxetine	1503	8.1 (7.7-8.5)
	Sertraline	786	5.1 (4.7-5.5)
	Venlafaxine	538	4.2 (3.8-4.6)
	Total	**4626**	**6.3 (6.1-6.5)**
Eudravigilance	Citalopram	144	3.1 (2.6 -3.6)
	Escitalopram	131	3.3 (2.8 - 4.0)
	Fluoxetine	200	4.9 (4.3 - 5.7)
	Fluvoxamine	48	4.0 (3.0 - 5.4)
	Paroxetine	535	8.6 (7.8 - 9.3)
	Sertraline	217	4.1 (3.6 - 4.7)
	Venlafaxine	244	3.6 (3.2 - 4.1)
	Total	**1519**	**5.1 (4.9 - 5.4)**

Prescription data

Table 2. Number of patients using SSRIs in the Netherlands between 2008 and 2012 [14].

Drug	2008	2009	2010	2011	2012
Citalopram	135,430	137,890	142,050	145,290	146,390
Escitalopram	32,351	37,778	45,232	52,480	55,338
Fluoxetine	57,341	54,350	52,961	52,807	52,653
Fluvoxamine	26,415	24,656	24,097	23,302	22,335
Paroxetine	230,470	214,670	204,330	196,670	191,100
Sertraline	51,810	52,476	55,559	58,532	63,009
Venlafaxine	121,740	115,090	113,220	111,820	111,260

Mechanism

SSRIs increase serotonergic activity in the central nervous system by inhibition of neuronal reuptake of serotonin. Serotonin is supposed to have a role in the inhibition of impulses, the regulation of emotions and social functioning, which are domains linked to aggression [10]. Several mechanisms are postulated by which

SSRIs might cause aggression. These include the production of feelings that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progress towards more severe agitation, aggression, and varying degrees of mania. Another proposed mechanism is the production of a combined state of stimulation and depression (an agitated depression) with a high risk of suicide and violence. Furthermore, the production of obsessive preoccupations with aggression against self or others, often accompanied by a worsening of any pre-existing depression. Finally, the production of akathisia, an inner agitation, that causes heightened irritability and frustration with aggression against self or others [13].
However, underlying disease and environmental influences make it difficult to demonstrate an indisputable relation between aggression and the use of SSRIs.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 78 reports of aggression associated with the use of SSRIs. Most reports were reported by consumers. In 24 reports the SSRI was reported as the only suspect drug and no other drugs or causes were reported. The reports show that the aggression experienced by some patients had a great impact on their lives.
The association of SSRIs with aggression is supported by a statistically significant disproportionality in the database of Lareb and the WHO and Eudravigilance. In the literature controversy exists about whether the SSRIs have a beneficial or harmful effect on aggression. Aggression is already mentioned in the SmPC of various SSRIs, except for fluoxetine, fluvoxamine and paroxetine. Since the seriousness of this association and the social unrest it causes it is recommended that this signal is also discussed in an international setting.

- Aggression should be mentioned in the SmPCs of fluoxetine, fluvoxamine and paroxetine
- Discussion of the signal in an international setting is warranted

References

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This signal has been raised on May 2014. 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).