

1.1. SSRIs and aggression

Introduction

The serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder.

SSRIs on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), paroxetine (Seroxat®), fluoxetine (Prozac®), sertraline (Zoloft®) and fluvoxamine (Fevarin®). Venlafaxine (Efexor®) in a dosage less than 150 mg is also considered an SSRI.

Recently, there has been much interest in the possible relation between aggression and the use of SSRIs. This is due to recent murder cases in the Netherlands, where a connection was made with SSRI usage [1].

The Dutch SmPCs of the SSRIs describe agitation and manic reaction as possible adverse drug reactions, but aggression and murder ideation are not described [2-7].

Reports

On June first 2009, the Lareb database of the Netherlands Pharmacovigilance Centre Lareb contained 24 reports of aggression or related ADRs associated with the use of SSRIs. The time to onset was one week or less in eight cases, 2-6 weeks in six cases, 1.5 year in one case and unknown in nine cases. It concerned the following SSRIs:

Paroxetine	8 cases
Citalopram	5 cases
Fluoxetine	4 cases
Fluvoxamine	4 cases
Escitalopram	2 cases
Sertraline	1 case

Table 1. Reports of aggression associated with the use of SSRIs.

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
A 10028 F, 29 General Practitioner	fluoxetine capsule 20mg		aggressive reaction	aggressive thoughts	6 days discontinued not reported
B 25667 M, 32 Pharmaceutical Company	fluvoxamine tablet 100mg		agitation, aggressive reaction, nausea	impulsive aggression	4 days discontinued not reported
C 27271 M, 76 Pharmaceutical Company	fluvoxamine tablet 50mg		hyperkinesia, amnesia, aggressive reaction, depersonalization, disorientation, hallucination visual	aggression	not reported unknown not reported
D 32622 F, 65 Pharmacist	paroxetine tablet 20mg Depressive episode	clonazepam tablet 0.5mg	hyperactivity, paranoid reaction, aggressive reaction	aggressiveness	3.1 weeks dose reduction recovered

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
E 34478 F, 18 Pharmacist	fluoxetine capsule 20mg	OAC tablet: ethinylestradiol /desogestrel	balance difficulty, aggressiveness	aggression	1 week discontinued unknown
F 36483 M, 10 Pharmaceutical Company	fluvoxamine tablet 50mg Depressive episode		suicidal tendency, aggressive reaction, irritability	physically aggressive	not reported discontinued unknown
G 37338 = 44991 = 37369 M, 33 Pharmaceutical Company	sertraline tablet 50mg		delusion, sensory hallucinations, psychotic reaction nos, aggressiveness	violent behavior, almost killing of girlfriend and 2-year-old son	3 days discontinued recovered
H 37487 M, 22 Pharmacist	fluoxetine tablet 20mg Burn		restlessness marked, thoughts of self harm, aggressive reaction	aggressive	day discontinued recovered
I 37696 M, 35 General Practitioner	paroxetine tablet 20mg Depressive episode		aggression aggravated	aggravation of aggressive symptoms	1,5 year discontinued recovered
J 37721 M, 11 Pharmacist	paroxetine tablet 100mg, ritalin tablet 10mg		sleep disorder, aggressiveness, self mutilation, character change	aggressive behavior	not reported discontinued recovered
K 37863 M, 23 Specialist doctor	fluvoxamine tablet 100mg Depression	lorazepam tablet 1mg risperidon tablet 1mg, biperidene tablet 2mg	aggressiveness	growing irritation, anger, aggression, resulting in homicide of his aunt and grandmother	6 weeks discontinued recovered
L 39137 M, 48 Specialist doctor	paroxetine tablet 40mg		aggressive reaction	severe impulse control disorder, resulting in fights. Attacked his boss; had to be stopped by 3 colleagues	several weeks no change unknown
M 39645 M, 34 General Practitioner	fluoxetine disp tablet 20mg Depressive episode		aggressiveness	verbal aggression, violence	not reported no change recovered
N 39646 M, 45 General Practitioner	citalopram tablet 40mg Depressive episode	diazepamum tablet 2mg	aggressiveness	verbal aggression	not reported unknown recovered

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
O 53709 M, 48 Consumer	paroxetine tablet 20mg Depression	bromazepam m tablet 3mg, venlafaxine tablet 75mg	suicidal tendency, aggressive reaction	aggressiveness	not reported discontinued not recovered
P 53981 F, 37 Consumer	citalopram tablet 20mg		aggressiveness, libido decreased	aggressive	not reported not reported unknown
Q 54840 M, 23 Consumer	citalopram drops 40mg/ml Anxiety	risperidon tablet 2mg	malaise, paranoia, aggressiveness	aggressive	1 day discontinued not recovered
R 57125 F, 28 Consumer	paroxetine tablet 20mg Depression		suicidal ideation, restlessness, aggressiveness, impulsive behaviour, self mutilation	aggression towards environment and herself, was placed in isolation cell	4 weeks dose reduction recovered
S 57704 M, 53 Consumer	paroxetine tablet 20mg		therapeutic response unexpected with drug substitution, aggressiveness	severe aggression	not reported no change recovered
T 60252 F, 39 Consumer	escitalopram tablet 10mg Depression	Salmeterol /fluticason 50/250mcg 60do	aggressiveness	aggressive behavior	4 weeks discontinued recovered
U 61293 M, 19 Consumer	citalopram tablet 40mg Psychiatric disorder NOS	risperidon tablet 4mg	suicidal ideation, aggressiveness	aggression	3 weeks no change not recovered
V 61981 F, 28 Consumer	escitalopram tablet 10mg Depression		myalgia, aggressiveness, galactorrhoea	aggression	4 weeks discontinued recovered
W 70367 M, 36 Pharmacist	paroxetine tablet 30mg Depression		food interaction, aggressiveness, impulse-control disorder	murder ideation towards son: temporary separation from kids	1 day unknown unknown
X 77918 M, 20 Hospital Pharmacist	citalopram tablet 40mg Depression		aggressive behavior	aggressive behavior: life- threatening for hospital staff	7 days no change unknown

Other sources of information

Literature

Although several studies describe a role for serotonin in aggression [8,9], there is no consensus in literature about the effect that the use of SSRIs may have on aggression. Some studies describe a direct link between use of SSRIs and increased violence and aggression [10-12] while other studies do not find any support for this association [13,14].

In a number of trials SSRIs have been investigated for the treatment of aggression. In a review on the pharmacotherapy of aggressive behaviour, of ten available placebo controlled RCTs with antidepressants six (four of which SSRIs) showed positive outcome for the antidepressant in clinically different groups of patients [15]. The conclusion is that there is weak evidence for the use of antidepressants in the management of aggression across a diversity of diagnoses.

Other databases

On June first 2009, the Lareb database of the Netherlands Pharmacovigilance Centre Lareb contained 24 reports of aggression or related ADRs associated with the use of SSRIs. This supports a causal relationship between SSRIs and aggression (ROR = 1.98; 95% CI 1.32 - 2.96). On June 30, 2009, the WHO database of the Uppsala monitoring centre contained 4,158 reports of aggressive reaction in association with SSRIs. This supports a causal relationship (ROR = 6.6; 95% CI 6.6 – 7.0).

On July 1st the Eudravigilance database contained 700 reports of aggression in SSRI using subjects. The reported reaction was reported serious in all but two cases. Sex was not specified in 16 cases, 387 male and 297 female patients were involved. Aggression formed part of a reaction leading to decease in 40 cases and led to disability in 36 cases. Patients' ages ranged from 3 to 90 years. Fifty-one patients were 12 years or younger of age.

Prescription data

The number of patients using SSRIs in the Netherlands is shown in Table 2.

Table 2. Number of users of SSRIs in the Netherlands between 2004 and 2008. (Source: Drug Information System of the Dutch Health Care Insurance Board (GIP))

	2004	2005	2006	2007	2008
N06AB serotonin reuptake inhibitors	568,820	548,490	547,090	523,790	556,060

Mechanism

SSRIs increase serotonergic activity in the central nervous system by inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).

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 [9].

Soon after starting treatment with SSRIs, akathisia, temporary increase in anxiety and/or paradoxical worsening of the individual's depressive agitation can occur; this may trigger for reactive aggressive behavior.

However, underlying disease and environmental influences make it difficult to demonstrate an indisputable relation between aggression and the use of SSRIs.

Conclusion

The Lareb reports suggest a possible relation between SSRIs and aggression. WHO data support this association. Special attention is asked for this association, considering the nature of the adverse drug reaction and the possible consequences.

References

1. Onderzoek rol antidepressiva in moordzaak. (version date: 23-6-2009, access date: 6-7-2009) <http://www.zielenknijper.nl/onderzoek-rol-anti-depressiva-in-moordzaak.html>.
2. Dutch SmPC of Seroxat[®]. (version date: 13-5-2009, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h14668.pdf>.
3. Dutch SmPC Cipramil[®]. (version date: 28-5-2008, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h19593.pdf>.
4. Dutch SmPC Prozac[®]. (version date: 2-4-2008, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h19429.pdf>.
5. Dutch SmPC Fevarin[®]. (version date: 6-2-2003, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h10245.pdf>.
6. Dutch SmPC Lepraxo[®]. (version date: 28-5-2008, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h30494.pdf>.
7. Dutch SmPC Zolof[®]. (version date: 18-3-2008, access date: 8-6-2009) <http://db.cbg-meb.nl/IB-teksten/h16292.pdf>.
8. Ryding E, Lindstrom M, Traskman-Bendz L. The role of dopamine and serotonin in suicidal behaviour and aggression. *Prog Brain Res.* 2008;172:307-15.
9. Krakowski M. Violence and serotonin: influence of impulse control, affect regulation, and social functioning. *J Neuropsychiatry Clin Neurosci.* 2003;15(3):294-305.
10. Breggin PR. Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (ssris): A review and analysis. *International Journal of Risk & Safety in Medicine* 2003;16:31-49.
11. Okada F, Okajima K. Violent acts associated with fluvoxamine treatment. *J Psychiatry. Neurosci.* 2001;26(4):339-40.
12. Healy D, Herxheimer A, Menkes DB. Antidepressants and violence: problems at the interface of medicine and law. *PLoS Med.* 2006;3(9):e372
13. Tauscher-Wisniewski S, Nilsson M, Caldwell C, Plewes J, Allen AJ. Meta-analysis of aggression and/or hostility-related events in children and adolescents treated with fluoxetine compared with placebo. *J Child Adolesc Psychopharmacol.* 2007;17(5):713-8.
14. Walsh MT, Dinan TG. Selective serotonin reuptake inhibitors and violence: a review of the available evidence. *Acta Psychiatr Scand.* 2001;104(2):84-91.
15. Goedhard LE, Stolker JJ, Heerdink ER, Nijman HL, Olivier B, Egberts TC. Pharmacotherapy for the treatment of aggressive behavior in general adult psychiatry: A systematic review. *J Clin Psychiatry* 2006;67(7):1013-24.

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