1.1. Serotonin Re-uptake Inhibitors (SSRIs) and alopecia

Introduction

Specific Serotonin Re-uptake Inhibitors (SSRIs) have been approved for marketing in the Netherlands for the treatment of one or more of the following indications: depressive episodes, obsessive-compulsive disorders, panic disorders, obsessive compulsive disorder, bulimia nervosa, diabetic neuropathic pain, social and generalized anxiety.[1-6]
Hair follicles go through a cycle starting with a growth stage or anagen phase before going into the resting stage or telogen phase, and then growing new hair again. Both anagen and telogen effluvium may be associated with SSRI associated alopecia. Either by inducing an abrupt cessation of mitotic activity in rapidly dividing hair matrix cells (anagen effluvium) or by precipitating the follicles into premature rest (telogen effluvium). In anagen effluvium, hair loss usually occurs within days to weeks of drug administration, whereas in telogen effluvium, hair loss becomes evident two to four months after starting treatment. Anagen effluvium is a prominent adverse effect of antineoplastic agents, which cause acute damage of rapidly dividing hair matrix cells. Telogen effluvium may be a consequence of a large number of drugs. Drug-induced hair loss is usually reversible after interruption of treatment. The prevalence and severity of alopecia depend on the drug as well as on individual predisposition.[19]
The Lareb database contains 1364 reports on alopecia as an adverse drug reaction. In 56 reports alopecia (MedDRA Preferred Term) is associated with treament with SSRIs. We received reports on all SSRIs currently marketed in the Netherlands. Alopecia is not listed in the SmPCs of paroxetine, fluvoxamine and citalopram. However alopecia is listed as common (0.1-1%) adverse reaction in the SmPC's of sertraline and escitalopram (the active S-(+)-enantiomer of citalopram) and is listed with unspecified frequency in the SmPC of fluoxetine. In this report, the association between the use of SSRIs and alopecia was analysed.

Reports

Until August 20, 2008 Lareb received 56 reports of alopecia (MedDRA Preferred Term) in association with SSRIs. Eight reports concerned males and at least 25 of the women were under the age of 50 (not all ages known). In almost 50% of the reports paroxetin was the suspected drug (also see Table 3). We received reports on all SSRIs currently marketed in the Netherlands which are listed in Table 1. None of the SSRIs shows a statistically significant association with alopecia in the Lareb database.

Table 1. Reports on SSRIs and alopecia in the Lareb and WHO database.

Drug	Number of reports	ROR (95% CI)
Citalopram	10	0.9 [0.5-1.8]
Escitalopram	1	
Fluoxetine	10	1.2 [0.6-2.1]
Fluvoxamine	4	0.5 [0.2-1.4]
Paroxetine	25	0.8 [0.5-1.2]
Sertraline	6	1.1 [0.5-2.5]

In 16 reports time to onset could not be ascertained. Of the other reports the time to onset was less than two months indicating anagen effluvium in 16 reports (5 fluoxetine, 10 paroxetine, 1 sertraline) and more than two months indicating telogen effluvium in the 24 remaining reports. In most notifications no information on outcome was reported. In only five reports, all concerning women, recovery after discontinuation - a positive dechallenge - was reported: citalopram three reports, fuoxetine one report and sertraline one report. These five reports are presented in more detail:

Report **A** is a well documented non-serious spontaneous report from a specialist on alopecia and pruritus in a female aged 83, which occurred 4 months after start of citalopram 10 mg and mirtazapine 15 mg. Co-medication: chlordiazepoxide, triamterene. Citalopram and mirtazapine were withdrawn and the patient recovered.
Report **B** is a moderately documented non-serious spontaneous report from a specialist on alopecia in a 35 year old woman, which occurred unspecified months after starting fluoxetine 20 mg daily for depression. As comedication nitrazepam and oxazepam were used. Fluoxetine was discontinued, whereafter patient recovered in several months.
Report **C** is a well documented non-serious spontaneous report from a specialist on alopecia in a 27-year-old woman, six months after starting sertraline 50 mg for depression. She used no concomitant medication. Patient recovered after discontinuation of sertraline; it was replaced by venlafaxine.
Report **D** is a well documented non-serious spontaneous report from a pharmacist which concerns a female aged 56 years, with alopecia following administration of citalopram 10 mg with a latency of 44 days after start. Concomitant medication was epoetine. Citalopram was withdrawn, patient recovered.
Report **E** is moderately documented non-serious spontaneous report from a pharmacist which concerns a female aged 64 years, with epistaxis, dizziness, stomatitis(blisters in the mouth) and alopecia following administration of citalopram for psychiatric disorder nos with a latency of 12 days after start. The symptoms appeared when the dosage was increased from 6 mg to 10mg and the patient recovered after the dosage was decreased to 6mg/ day. Later, the drug was withdrawn. Concomitant medications were diclofenac/misoprostol and sumatriptan, both used as necessary, but concomitant medication was not used during treatment with citalopram.

Other sources of information

Literature

Hedenmalm et all studied all reports of alopecia with marketed SSRIs until the end of 2004 in SWEDIS, the national Swedish database for spontaneously reported ADRs, and in Vigibase, the international ADR database of the World Health Organization. A total of 27 reports of alopecia were identified in SWEDIS. As two reports concerned the use of two SSRIs, there was a total of 29 drug-ADR combinations. All except three reports concerned women (88.9%). The reporting rate of alopecia in Sweden was significantly higher with sertraline compared with citalopram; 20.1 (95%CI 10.7-34.4) reports per million patient-years versus 4.5 (95%CI 1.8-9.3) reports per million patient-years. No significant differences in reporting rates were noted for the remaining SSRIs. Sertraline also showed a statistically significant association with alopecia in both SWEDIS and Vigibase. Citalopram was significantly associated with alopecia in Vigibase, but not in SWEDIS. No statistically significant associations were found for any of the other SSRIs.[7]
Case-reports have been published on alopecia associated with treatment with paroxetine [8,9], fluvoxamine [10], sertraline [11] and fluoxetine. [12-14] This suggests a group effect but there are indications that individuals may have different sensitivities for alopecia as an adverse reaction depending on SSRI. [15,16] Paradoxically paroxetine and fluoxetine may also cause hirsutism or hypertichosis.[17]

Databases

The distribution of reports of alopecia associated with SSRIs in the WHO database (Vigibase) is comparable to the distribution in the Lareb database (see Table 1 and 2). Citalopram and Sertraline show a statistically significant association with alopecia as previously reported by Hedenmalm et al.[7]

Table 2. Reports on SSRIs and alopecia in the WHO database.

Drug	Number of reports	ROR (95% CI)
Citalopram	164	2.0 [1.7-2.3]

Drug	Number of reports	ROR (95% CI)
Escitalopram	29	1.5 [1.0-2.1]
Fluoxetine	264	0.8 [0.7-0.9]
Fluvoxamine	40	0.9 [0.7-1.3]
Paroxetine	250	1.0 [0.9—1.2]
Sertraline	461	2.4 [2.2-2.6]

The proportional number of notifications of alopecia associated with SSRIs in the Lareb database corresponds with the proportional number of users of SSRIs in the Netherlands as listed in Table 3

Table 3. Number of users of SSRIs in the Netherlands.

Drug	2003	2004	2005	2006	2007
Citalopram	101,280	121,090	126,850	125,200	129,920
Escitalopram	.	702	9,606	19,608	27,604
Fluoxetine	72,348	71,066	66,343	66,350	60,530
Fluvoxamine	38,457	36,687	33,250	32,497	28,785
Paroxetine	304,380	303,580	277,040	277,800	248,980
Sertraline	48,076	57,657	56,032	59,500	55,073

Source: GIP/College for health insurances 2008 Updated : May 6, 2008

Mechanism

It has been shown that human skin can produce serotonin and transform it into melatonin. Melatonin has in turn been implicated in hair growth cycling. It is, therefore, possible that treatments that interfere with the serotonin homeostasis in the skin may alter the balance between hair growth and hair shedding.[18]
It has also been suggested that antimitotic activity asserted by SSRIs may play a role.[17]

Discussion and conclusion

Alopecia can have many causes which makes causality assessment of putative ADRs difficult. Nevertheless alopecia is listed in the SmPCs of some, but not all SSRIs currently marketed in the Netherlands. Lareb received notifications on all SSRIs currently marketed in the Netherlands with the majority of reports concerning women. Citalopram and Sertraline show a statistically significant association with alopecia in the WHO database (Vigibase) but not in the Lareb database. Reported times to onset in the lareb database are compatible with both anagen and telogen effluvium. Although the exact mechanism of SSRI-associated alopecia is not clear recovery after discontinuation was reported in 5 of 56 reports.
Notifications as well as case-reports from literature suggests a group effect but there are indications that individuals may have different sensitivities for alopecia as an adverse reaction; depending on SSRI (see report C).

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This signal has been raised on December 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).