

1.1. Paroxetine and gynaecomastia

Introduction

Paroxetine (Seroxat®) was granted marketing authorization in 1991 in the Netherlands. Paroxetine is indicated for the use in *depression, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social anxiety disorder/social phobia, generalized anxiety disorder and posttraumatic stress disorder* [1].

The efficacy of paroxetine in the treatment of the indications mentioned above is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake [1].

Other SSRI's available on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Fevarin®) and sertraline (Zoloft®).

Gynecomastia, a benign proliferation of the glandular tissue of the male breast, is caused by an increase in the ratio of estrogen to androgen activity. It may be unilateral or bilateral and is diagnosed on exam as a palpable mass of tissue at least 0.5 cm in diameter (usually underlying the nipple). Gynecomastia differs from female breast development in that there is no progesterone-induced terminal alveolar development. Physiologic gynecomastia, which resolves spontaneously in most cases, has a trimodal distribution, occurring in neonatal, pubertal, and older males. The estimated prevalence of asymptomatic gynecomastia in these three age groups is 60 to 90 percent in neonates, 50 to 60 percent in adolescents, and 35 to 65 percent in men ages 50 to 69 years. The causes of gynecomastia among adult men can be either physiologic or pathologic and include persistent pubertal gynecomastia, cirrhosis or malnutrition, hypogonadism, testicular tumors, hyperthyroidism and chronic renal insufficiency. In 10 to 25 percent of cases drugs are seen as a cause. There are many drugs that have been associated with gynecomastia. Drugs with the best evidence for an association with gynecomastia include spironolactone, cimetidine, ketoconazole, recombinant human growth hormone, estrogens, human chorionic gonadotropin (hCG), anti-androgens, gonadotropin-releasing hormone (GnRH) agonists, and 5-alpha-reductase inhibitors. In another 25 percent of cases no detectable abnormality (idiopathic) is found. Pseudogynecomastia, which is often seen in obese men, refers to fat deposition without glandular proliferation. Gynecomastia must be differentiated from breast carcinoma, which is far less common [2].

Reports

From 09-02-1998 until 12-10-2015, the database of the Netherlands Pharmacovigilance Centre Lareb contained 12 reports of gynaecomastia associated with the use of paroxetine. The reports are listed in table 1.

Table 1. Reports of gynaecomastia associated with paroxetine use in the Lareb database

Patient, Number, Sex, Age, Source, BMI	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 20112 M, 61-70 years, General Practitioner BMI unknown	paroxetine 20mg , 1 dd1 Depressive episode	atenolol, cimetidine	gynaecomastia	6 Months, Dose not changed,
B, 21512 M, 41-50 years, General Practitioner BMI unknown	paroxetine 20mg, 1 dd 1, Depressive episode	simvastatin , acetylsalicylic acid	gynaecomastia	9 Months, Dose not changed,
C, 25635 M, 41-50 years, Pharmacist BMI unknown	paroxetine 20mg 1dd1		gynaecomastia ,galactorrhoea	12 Weeks, Drug withdrawn,
D, 32788 M, 31-40 years, General Practitioner BMI unknown	paroxetine 20mg 1dd1 Depressive episode		gynaecomastia	10 Months, Dose not changed, Unknown

E,34380 M, 21-30 years, General Practitioner BMI unknown	paroxetine 20mg 1dd1 Panic attacks		gynaecomastia	2 Years, Dose not changed, Unkn
F, 39838 M, 41-50, years, Pharmacist BMI unknown	ranitidine tablet 300mg 1dd1, pantoprazol 40 mg, 1dd1, paroxetine 20mg 1dd1	oxazepam	gynaecomastia	Pantoprazole: Drug withdrawn, Paroxetine: Dose not changed, Ranitidine: Drug withdrawn, Not recovered/not resolved
G, 52873 M, 61-70 years, General Practitioner BMI 24.7	paroxetine 20mg 1dd1, Depression	rabeprazole	gynaecomastia	4 Months, Drug withdrawn, Recovered/resolved
H, 61547 M, 51-60, year, General Practitioner BMI 25.3	paroxetine 20mg 1dd1, Depression	atenolol, oxazepam	gynaecomastia	5 Years, Dose not changed, Unknown
I, 80833 M, 31-40 years, General Practitioner BMI 26.4	paroxetine 20mg 1dd1 Depression	oxazepam	gynaecomastia	8,5 Months, Dose not changed, Unknown
J 106336 M, 71 years and older, Pharmacist BMI unknown	paroxetine 20mg 1dd1		gynaecomastia	4 Months, Dose not changed, Unknown
K 127531 M, 61-70 years, General Practitioner BMI 23.4	itraconazole capsule 100mg, 2dd1 Paronychia, paroxetine 20mg 1dd1 Depression		gynaecomastia	Itraconazole 2 Months, Drug withdrawn, Not recovered/not resolved Paroxetine 10 years Dose not changed, Not recovered/not resolved
L, 201166 M, 71 years and older, General Practitioner BMI 25.9	paroxetine tablet 20mg 1dd1, Mood disorder NOS		gynaecomastia	8 Months, Drug withdrawn, Recovering/resolving

Additional information about the cases is listed below.

Case A. Gynaecomastia consisted of a small round disc with a diameter of 7 cm.

Prolactin levels 0.66 (normal value lab. Is 0-0.4) The dose of paroxetine was reduced-dose, outcome is unknown. The gynaecomastia developed left-sided. Cimetidine, for which gynaecomastia is a known adverse drug reaction [3], is listed as concomitant medication. The reporter mentions however that this drug was used sporadically.

Case B. The prolactin level has been determined and is 'normal'. No blood-levels are present in the report.

Case C. Gynaecomastia consisted of a painful and enlarged right breast, once there was a watery galactorrhoea.

Case D. The gynaecomastia was right-sided.

Case E. The gynaecomastia consisted of a small gland on the slice left; nothing could be palpated on the right, however this side felt sensitive upon touch.

Case F. Other suspect medications ranitidine and pantoprazole are both rare causes of gynaecomastia [4,5]. However, these drugs were withdrawn and five months later the gynaecomastia was still present and getting worse.

Case G. Concomitant drug rabeprazole is a rare cause of gynaecomastia [6].

Case I. Paroxetine dose was not changed but oxazepam was withdrawn. The patient outcome is unknown. Previously the gynaecomastia while using paroxetine was treated by liposuction but it returned.

Case J. The gynaecomastia was described as a glandular disk of 11x12cm bilaterally, giving the patient a cup A breast size. The gynaecomastia disappeared after switching to another brand of paroxetine (unknown if there was a dosage change as well).

Other sources of information

SmPC

The Dutch SmPC of paroxetine (Seroxat®) mentions (incidence rare) hyperprolactinaemia/galactorrhoea, menstrual diseases (including menorrhagia, metrorrhagia, amenorrhoea and delayed or irregular menstruation) [1]. This is also reflected in the patient information leaflet (PIL), where abnormal production of milk in both men and women is mentioned. Gynaecomastia is not mentioned in both the SmPC nor the PIL.

Literature

The Dutch handbook '*Informatorium Medicamentorum*', maintained by the Dutch Royal Pharmacist Association (KNMP) mentions for the SSRIs as a group: *Gynecomastia has been reported from three months to two years after starting treatment; this did not seem to be due to an increase in prolactin levels* [7].

The association has been described in the literature for paroxetine as well as for other SSRIs [8-13]. Ekman and Dobs [10] describe in their review on drug-induced gynaecomastia that it has been (rarely) described for SSRIs and SNRIs and that described prolactin levels are within normal to mildly increased ranges.

Some case-reports are described in more detail below: A 30 year old man had been followed since age 19 for panic disorder with agoraphobia. After a major depressive episode at the age of 25, the patient began psychotherapy and was started on paroxetine, 40mg daily. Several months later, he noticed that his left breast was slightly enlarged, but waited almost 5 years before reporting this to his physician. In addition to paroxetine, the patient used incidentally diazepam but was not taking any other concomitant medication. The breast examination revealed overt enlargement of the left breast with minimal enlargement of the right breast. Prolactin concentration was 14ng/ml. (normal range 4.1 - 18.5ng/ml). Biopsy showed no evidence of malignancy. The gynecomastia was reduced by surgery and paroxetine was replaced with mirtazapine. At 2 year follow up there was no evidence of recurrence [9].

A 67-year-old male presented with new-onset gynecomastia and breast tenderness. Mammography revealed bilateral gynecomastia (fibroglandular tissue posterior to the nipples bilaterally) without suspicious mass, calcification, or other abnormalities. These new symptoms developed after sertraline was added to his stable medication regimen (duloxetine, alprazolam, rosuvastatin, metoprolol, amlodipine, hydrochlorothiazide/triamterene, metformin, and sitagliptin). These symptoms were dose-dependent, with gynecomastia and breast tenderness more severe as sertraline was titrated from 25 mg/day to 50 mg/day and then to 75 mg/day. While there also maybe an effect of duloxetine, when sertraline was discontinued, gynecomastia and breast tenderness rapidly resolved [11].

It is important to note that also unilateral gynaecomastia has been described with SSRI use. For instance, 19-year-old man noticed a unilateral (left) gynecomastia without galactorrhea while three months on venlafaxine therapy. Laboratory tests revealed increased serum prolactin, estradiol, and luteinizing hormone levels. Drug withdrawal led to a reduction of the lump, and the hormone levels were all in reference range [13].

Databases

Table 2. Reporting odds ratios of paroxetine and gynaecomastia in the database of the Netherlands Pharmacovigilance Centre Lareb, the WHO and the Eudravigilance (EMA) database [14,15]

Drug and ADR	Number of reports	ROR (95% CI)
Paroxetine and gynaecomastia	Lareb: 12	2.5 (1.4-4.4)
	WHO: 74	0.9 (0.7-1.1)
	Eudravigilance: 26	1.4 (0.9-2.0)

Prescription data

Table 3. Number of paroxetine users in the Netherlands between 2011 and 2014 [16].

Drug	2011	2012	2013	2014
Paroxetine	196,670	191,190	184,960	181,420

Mechanism

SSRIs can produce changes in dopaminergic neurotransmission and hyperprolactinemia due to adaptive changes in dopaminergic neurons.

Two mechanisms for selective serotonin reuptake inhibitors (SSRIs) to cause gynaecomastia have been proposed; Through presynaptic inhibition of dopamine release by serotonergic neurons or prolactin release by direct stimulation of postsynaptic serotonergic receptors in the hypothalamus have been described [8,9,17,18]. The latter mechanism will also lead to hyperprolactinemia.

Discussion and conclusion

Lareb received a total of 12 reports of gynaecomastia associated with the use of paroxetine. The association is disproportionately present in the Lareb database. Men ages 50 to 69 years have a higher chance of developing gynaecomastia, but Lareb also received five reports in younger men. The patient's weight could be seen as a contributing factor, patient's BMI is known in five cases and ranges from 23.4-26.5 kg/m². Unfortunately we have no information on other contributing factors like (excessive) alcohol use. In some cases an unilateral gynaecomastia was reported, but this has also been described in the literature. One patient experienced galactorrhoea as well as gynaecomastia. Prolactin levels were increased in 1 case and within the normal range in another case (however not specified in the latter). In the literature, gynaecomastia with prolactin levels in the normal range have been described [8].

Lareb also received 7 cases of gynaecomastia for other SSRIs, namely citalopram (n=4), sertraline (n=2), fluvoxamine (n=1). Based on the literature [9-13] and the mechanisms proposed in the literature, a class-effect seems likely. However, these cases were deemed not strong enough to warrant a signal as a group-effect.

Although healthcare professionals might relate the occurrence of gynaecomastia in a patient to hyperprolactinaemia, which is described in the SmPC [1], for patients it is not clear that gynaecomastia could be a result of paroxetine use.

Galactorrhoea and menstrual diseases, both related to hyperprolactinaemia, are specified in the SmPC and PIL. Because gynaecomastia can be an equally important ADR to patients as galactorrhoea, this could also be specifically mentioned in the SmPC and subsequently in the PIL.

- Gynaecomastia should be labelled in the SmPC of paroxetine and subsequently in the PIL

References

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This signal has been raised on January 2016. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl