

Short communication

Breast enlargement during chronic antidepressant therapy

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Abstract

Recent reports of mammoplasia during selective serotonin re-uptake inhibitor (SSRI) therapy suggested that this side effect may be more common than previously reported. We examined 59 women receiving ≥ 2 months treatment with an SSRI or venlafaxine for changes in breast size in relation to menopausal status, weight gain and duration of drug therapy. Serum prolactin, estradiol and beta-hCG were also measured before and during treatment in a subgroup of patients. Twenty-three out of 59 patients (39%) reported some degree of mammoplasia. Significantly more SSRI vs. venlafaxine patients reported mammoplasia ($p < 0.01$). Eighty-four percent with mammoplasia had weight gain vs. 30% without mammoplasia ($p < 0.001$). The rate of mammoplasia was unrelated to age, menopausal status or duration of treatment. Serum prolactin increased during treatment in the paroxetine subgroup ($p < 0.03$). In conclusion, antidepressant-induced mammoplasia may be more common than previously expected. © 1997 Elsevier Science B.V.

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1. Introduction

Reports of antidepressant-induced gynecomastia (breast enlargement in men) or mammoplasia (breast enlargement in women) are infrequent (Klein et al., 1964; Arroyo, 1966; Margolis and Gross, 1967; Shader and DiMascio, 1970; Anand, 1985; Uehlinger

and Baumann, 1991; Bronzo and Stahl, 1993; Hall, 1994). While most commonly associated with neuroleptic use (Hyman and Arana, 1987), breast enlargement has been noted with tricyclic (Klein et al., 1964; Anand, 1985), monoamine oxidase inhibitor (Arroyo, 1966) and SSRI (Bronzo and Stahl, 1993; Hall, 1994) antidepressants. The cause of antidepressant-induced breast enlargement is not clear, although subtle perturbations in pituitary and/or peripheral hormone release (Markan et al., 1992; Jeffries et al., 1992; Thompson and Carter, 1993) and generalized weight gain during chronic antide-

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pressant therapy might contribute to the presence of breast enlargement.

We recently have been struck by spontaneous reports of mammoplasia in some women on chronic SSRI therapy. These complaints have ranged from a subjective sense of breast fullness to an observable increase in bra and/or bra cup size. While gynecomastia is easily recognized, we wondered whether more subtle degrees of mammoplasia might go unrecognized or unreported.

This study examined the frequency of patient-reported mammoplasia during chronic SSRI and venlafaxine therapy.

2. Methods

2.1. Subjects

We examined 59 female outpatients with a mean (\pm S.D.) age of 47 ± 13 years (range 23–80 years) taking fluoxetine ($n = 8$), sertraline ($n = 4$), paroxetine ($n = 28$) or venlafaxine ($n = 19$) at recommended doses for ≥ 2 months (Table 1). All patients were diagnosed with major depressive episode (39 unipolar, 20 bipolar) (American Psychiatric Association, 1988). 32 were premenopausal and 27 postmenopausal (with or without estrogen replacement therapy), and all were in good physical health without chronic medical illnesses. All were euthyroid by laboratory tests, and none had a history of breast cancer, mastectomy, breast augmentation or reduction surgery, chronic mastitis or galactorrhea. None of the women were taking medications known to

produce breast enlargement (e.g. neuroleptics or corticosteroids), although several were taking oral contraceptives, estrogen replacement or l-thyroxine.

A comparison group of 322 depressed women were examined to estimate potential differences in reported mammoplasia rates when symptom information was collected by physician-elicited versus patient-reported methods. The comparison group was consecutively selected from 577 women who previously participated in a multi-center, fixed-dose (20 mg daily for ≥ 2 months) fluoxetine trial (Amsterdam et al., 1997).

2.2. Clinical assessments

The presence or absence of mammoplasia was physician-elicited in the index group and patient-reported in the comparison group, and tabulated as (a) subjective sense of breast fullness and/or discomfort, and (b) an increase in bra size and/or bra-cup size. Change in body weight was determined as actual weight measurements made prior to and during treatment, or as patient-reported weight change during treatment.

2.3. Laboratory procedures

Measurements of serum prolactin, estradiol and beta-hCG before and during treatment were available from a subgroup of 16 patients. All hormone assays were performed in batch. Prolactin was quantified using a two site chemiluminometric (sandwich) immunoassay ACS:180. The ACS prolactin assay is standardized against the World Health Organization

Table 1
Demographic features of treatment groups

	All patients	Paroxetine	Fluoxetine	Sertraline	Venlafaxine
Number	59	28	8	4	19
Age (years)					
mean \pm S.D.	47.3 ± 13.0	50.0 ± 11.4	48.9 ± 18.4	37.0 ± 7.0	44.8 ± 13.1
(range)	(23–80)	(26–73)	(23–73)	(31–46)	(26–80)
Treatment duration (months)					
mean \pm S.D. ^a	9.7 ± 7.4	8.9 ± 4.9	14.6 ± 14.8	15.0 ± 7.7	7.8 ± 4.9
(range)	(2–48)	(2–18)	(3–48)	(6–24)	(2–18)
Daily dosage (mg)					
mean \pm S.D.	–	27 ± 11	24 ± 7	122 ± 69	171 ± 107
(range)		(10–50)	(20–40)	(138–200)	(37.5–500)

^a ANOVA $F_{(3,58)} = 2.58$, $p = 0.07$.

3rd IRP 84/500 reference material. Estradiol was quantified by immunoassay using the Diagnostics Product Corporation Coat-A-Count TKE assay system. Total beta-hCG was assayed in a microparticle immunoassay (Abbot IMX).

2.4. Statistical procedures

Group comparisons were performed using analysis of variance (ANOVA), while categorical comparisons were made using X^2 analysis or Fisher's Exact test. Paired t -tests were used to compare differences in mean hormone concentrations. All statistical results were interpreted as two-tailed with significance set at $p < 0.05$.

3. Results

Twenty-three out of 59 patients (39%) reported some degree of mammoplasia. Of these, 53% reported a subjective sense of breast fullness or discomfort, while 47% reported an increase in bra and/or bra-cup size. None of the women reported galactorrhea, tenderness or a reduction in breast size.

64% of paroxetine patients reported mammoplasia compared to fluoxetine (25%), sertraline (25%) and venlafaxine (11%) patients ($X^2 = 15.0$, $df = 3$, $p < 0.01$) (Table 2), although this difference failed to achieve statistical significance when only the SSRI groups were compared ($X^2 = 5.2$, $df = 2$, $p < 0.08$).

The mammoplasia rate appeared to be lowest in venlafaxine compared to SSRI-treated patients ($X^2 = 7.9$, $df = 1$, $p < 0.01$).

Data on weight change during treatment was available from 52 subjects (Table 3). Weight increase from 4 to 30 lbs was seen in 50% of the patients. Sixty-two percent of women with weight gain had mammoplasia compared to 12% of women without weight gain. Similarly, 84% of women with mammoplasia experienced some weight gain compared to 30% of women without mammoplasia ($X^2 = 11.9$, $df = 1$, $p < 0.001$). Thus, while some patients experienced mammoplasia without weight gain, most women with mammoplasia had concurrent weight gain, suggesting a relationship between these factors. Interestingly, the mean weight gain was similar in patients with (12.5 ± 5.1 lbs) and without (11.4 ± 10.4 lbs) mammoplasia [$p = \text{n.s.}$ (not significant)].

Treatment duration was found to have little effect on mammoplasia rates among treatment groups ($p < 0.07$), while similar rates of mammoplasia were observed in premenopausal (31%) and postmenopausal (52%) women ($X^2 = 1.8$, $df = 1$, $p = \text{n.s.}$).

While no differences in mean estradiol or beta-hCG values were observed in the subgroup of 16 women (Table 4), we observed a modest increase in mean prolactin during treatment among all subjects ($p < 0.08$), and a statistically significant increase in the paroxetine-treated patients ($p < 0.01$) (Table 5).

Finally, in contrast to our observation of a mam-

Table 2
Rates of breast enlargement during treatment^a

Breast enlargement	All patients	Paroxetine	Fluoxetine	Sertraline	Venlafaxine
Present % (<i>n</i>)	39% (23)	64% (18) ^c	25% (2)	25% (1)	11% (2) ^b
Absent % (<i>n</i>)	61% (36)	36% (10)	75% (6)	75% (3)	89% (17)

^a Overall $\chi^2 = 15.0$, $df = 3$, $p < 0.01$.

^b All SSRIs vs. Venlafaxine: $\chi^2 = 11.3$, $df = 1$, $p < 0.001$.

^c Paroxetine vs. Venlafaxine: $\chi^2 = 11.3$, $df = 1$, $p < 0.001$.

Table 3
Weight gain during treatment

Weight gain	All patients	Paroxetine	Fluoxetine	Sertraline	Venlafaxine
Present % (<i>n</i>)	50% (26)	58% (14)	57% (4)	75% (3)	30% (5)
Absent % (<i>n</i>)	50% (26)	42% (10)	43% (3)	25% (1)	70% (12)

Overall $\chi^2 = 4.70$; $df = 3$; $p = \text{n.s.}$ (not significant).

Table 4
Hormone concentrations in all treatment groups ($n = 16$)

	Pre-treatment	Post-treatment	Δ value	t value	p value
Prolactin (ng/ml)	6.6±2.7 (1.6–11.1)	9.3±7.0 (4.0–31.2)	2.7±5.7 (–3.5–21.7)	1.91	0.08
Estradiol (pg/ml)					
Pre-menopausal ($n = 5$)	33.9±36.6 (1–89.8)	27.4±39.3 (1–94.9)	–6.5±45.2 (–61.9–60)	0.32	n.s.
Post-menopausal ($n = 11$)	22.3±43.7 (1–150)	19.1±43.7 (1–150)	–2.9±10.7 (–34.4–5.9)	0.89	n.s.
hCG (mIU/ml)					
Pre-menopausal ($n = 5$)	11.2±17.3 (1–40.9)	18.1±23.8 (1–50)	6.9±11.0 (0–25.4)	1.41	n.s.
Post-menopausal ($n = 11$)	15.2±18.9 (1–47.4)	21.6±35.6 (1–119)	6.3±25.9 (–29.2–77)	0.82	n.s.

Table 5
Hormone concentrations in paroxetine treatment groups ($n = 8$)

	Pre-treatment	Post-treatment	Δ value	t value	p value
Prolactin (ng/ml)	5.8±3.0 (1.6–11.1)	8.4±4.4 (4.0–17.8)	2.5±2.2 (–0.3–6.7)	3.28	0.01
Estradiol (pg/ml)					
Pre-menopausal ($n = 1$)	89.8	27.9	–61.9		
Post-menopausal ($n = 7$)	11.3±12.6 (1–36.4)	5.9±5.7 (1–12)	–5.4±12.9 (–34.4–0.1)	1.11	n.s.
hCG (mIU/ml)					
Pre-menopausal ($n = 1$)	1.0	1.2	0.20		
Post-menopausal ($n = 7$)	10.8±14.6 (1–42)	24.1±42.4 (1–119)	13.3±28.9 (–1.7–77)	1.21	n.s.

moplasia rate of 25% in fluoxetine-treated patients in the present study, there were no patient-reported cases of breast enlargement in 322 women treated with fluoxetine (> 2 months) from the multi-center trial ($p < 0.001$). Thus, mammoplasia rates appear to be partly influenced by the method of data acquisition.

4. Discussion

While drug-induced gynecomastia and mammoplasia is generally held to be infrequent (Klein et al., 1964; Arroyo, 1966; Shader and DiMascio, 1970; Anand, 1985; Bronzo and Stahl, 1993; Hall, 1994), our observation of a 39% mammoplasia rate in women taking SSRIs and venlafaxine suggests that

this side effect may be under-reported by patients and physicians.

In this study, paroxetine demonstrated the highest mammoplasia rate when compared with other SSRIs ($p < 0.01$) or venlafaxine ($p < 0.001$). Although our samples sizes are limited, one possible explanation for the higher rate with paroxetine might be its greatest degree of serotonin re-uptake inhibition in comparison with other SSRIs and venlafaxine (Thomas et al., 1987). If so, this factor might partly account for our observation of a higher rate of mammoplasia with paroxetine (64%) compared to other SSRIs (25%) and venlafaxine (11%).

Alternatively, SSRI-induced perturbations in hormone secretion and/or changes in normal fatty tissue metabolism might contribute to mammoplasia. In this context, SSRIs have been shown to increase prolactin secretion (Jeffries et al., 1992; Shapira et

al., 1992; Gilmore et al., 1993) possibly through alterations in dopamine neurotransmission (Molitch, 1992). Neuroleptic-induced increases in prolactin have also been associated with galactorrhea and mammoplasia (Kirby et al., 1979; Meltzer and Fang, 1986).

In addition, SSRIs may alter normal fatty tissue metabolism thereby increasing deposition of fatty tissue, resulting in weight gain (Spring et al., 1995). This process may be enhanced by perturbations in hormone secretion (Shapira et al., 1992; Gilmore et al., 1993), and may be gender-specific occurring at sites of high fatty tissue distribution (accounting for the rarity of antidepressant-induced gynecomastia in men).

Several caveats should be considered in the interpretation of the present observations. One obvious limitation is the lack of a placebo control group and the naturalistic fashion in which the data were collected. Thus, our observations are based upon patient reports rather than breast size measurements, and the subjective nature of these data may have introduced bias resulting in inflated mammoplasia rates. Furthermore, our failure to identify any cases of mammoplasia in 322 women prospectively treated with fluoxetine in a multi-center study suggests that different data acquisition techniques can strongly influence results. While the present observations do suggest that mild degrees of mammoplasia may be more frequent during SSRI treatment than previously reported (Bronzo and Stahl, 1993; Hall, 1994), a prospective study of direct breast size measurement would provide more accurate information on drug-induced mammoplasia.

Finally, the dose of medication in each group was not fixed over the course of treatment, and it is possible that the presence of mammoplasia may be dose-dependent, increasing in frequency with higher doses. This might be one explanation for the paucity of mammoplasia reported in the sample of 322 women treated in the fluoxetine, fixed-dose (20 mg daily), multi-center trial.

In conclusion, 39% of women taking chronic SSRIs or venlafaxine reported some degree of mammoplasia. This rate is substantially higher than previously expected. The highest rates of mammoplasia was reported with paroxetine (64%) when compared with other SSRIs and venlafaxine ($p <$

0.01). While mammoplasia is associated with generalized weight gain, it does not appear to be related to age, menopausal status or duration of antidepressant treatment.

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