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Bupropion and SSRI-induced side effects

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) are a first line treatment option for millions of patients, due to the positive balance between efficacy and tolerability. However, some side effects associated with their use, can impair quality of life and compliance with treatment. This paper reviews the prevalence of sexual dysfunction, weight gain and emotional detachment during SSRI treatment, the profile of bupropion for each of these events and the ability of bupropion to reverse them. Double-blind trials, open-label trials and anecdotical reports derived from Medline were included. First, there is robust evidence that SSRIs can induce sexual side effects and that bupropion causes less sexual dysfunction than SSRIs. There is limited, mainly open-label evidence that bupropion can reverse SSRI-induced sexual side effects. Second, there is good evidence that long-term treatment with some SSRIs can result in weight gain and that long-term treatment with bupropion can result in a small weight loss. There is only anecdotical evidence that bupropion can reverse SSRI-induced weight gain. Third, treatment with SSRIs has been associated with 'emotional detachment', although controversy exists about this concept. No data are available on the profile of bupropion for 'emotional detachment' or for the reversal of SSRI-induced 'emotional detachment' by bupropion-addition.

Keywords

bupropion, serotonin reuptake inhibitors, sexual dysfunction, weight gain, emotional detachment

Introduction

Patients with major depressive disorder frequently need long-term pharmacological treatment, especially those with recurrent or severe depressive episodes (Bauer *et al.*, 2002a; 2002b).

Unfortunately, 32–60% of patients discontinue their pharmacotherapy in the first three months, often without informing their physician (Myers and Branthwaite, 1992; Simon *et al.*, 1993; Maddox, 1994; Demyttenaere *et al.*, 2001; Olfson *et al.*, 2006). In naturalistic studies, the most frequent reasons for discontinuation seem to be 'feeling better' and 'adverse events' (Maddox, 1994; Demyttenaere *et al.*, 2001).

Not only physical side effects like sexual dysfunction and weight gain have been associated with serotonin reuptake inhibitors (SSRIs), but also more subtle psychological side effects like emotional detachment or sanguinity (Hoehn-Saric *et al.*, 1990; Healy, 2000; Opbroek *et al.*, 2002; Bolling and Kohlenberg, 2004; Lee and Keltner, 2005). Psychological side effects seem to be cited just as often as physical side effects as the primary reason for quitting SSRI therapy (Bolling and Kohlenberg, 2004).

It is often unclear why physicians prescribe a particular antidepressant and whether this choice is influenced by scientific grounds (i.e., pharmacological profile resulting in differential efficacy for particular patients or resulting in a differential side-effect profile), or by pharmaco-economic considerations, or by influences from marketing departments (positioning of the antidepressant by the pharmaceutical industry).

Bupropion is the only antidepressant with a dual effect on norepinephrine and dopamine neurotransmitter systems with no known serotonergic activity (Stahl *et al.*, 2004) and was initially developed to improve on the safety and tolerability of existing antidepressants (Fava *et al.*, 2005). A recent survey revealed that the wish to avoid specific side effects, like sexual dysfunction, weight gain and fatigue is the most important reason why this agent is prescribed by physicians (Zimmerman *et al.*, 2005).

The present paper focuses first, on the prevalence of sexual dysfunction, weight gain and emotional detachment during SSRI therapy; second, on the profile of bupropion for these events; and third, on the available evidence for the reversal of SSRI-induced side effects by bupropion-addition.

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Methods

The literature included in this review was drawn from the Medline database. For the review of prevalence of SSRI-induced sexual dysfunction, following search terms were used: 'SSRI' or the pharmacological names of the separate SSRIs, 'antidepressive agents', 'prevalence', 'incidence', 'sexual dysfunction' and 'sexual function'. For the section on bupropion and sexual side effects, 'bupropion', 'incidence', 'prevalence', 'sexual dysfunction' and 'sexual function' were used as search terms. Papers on add-on therapy for SSRI-induced sexual side effects were identified using the terms 'bupropion', 'sexual dysfunction' or 'sexual function' and 'addition' or 'add-on'. Only papers written in English and with an adult target population were included. The same search strategy was used in the sections on weight gain and emotional blunting during antidepressive treatment, except in the latter section where also papers with a paediatric population were included. Finally, relevant papers identified from reference lists were added.

Results

Sexual side effects

Prevalence of SSRI-induced sexual side effects Despite the fact that serotonergic agents are frequently associated with a substantial risk of sexual side effects (Segraves, 1998; Montejo *et al.*, 2001; Clayton *et al.*, 2002; Fava and Rankin, 2002), the exact prevalence of SSRI-induced sexual dysfunction is not known. A wide range of prevalence estimates have been reported, ranging from very low percentages to more than 80% (Rosen *et al.*, 1999). Several methodological issues complicate the search for a reliable prevalence-estimate, and make it difficult to compare the numerous reports in the field (Baldwin, 2001; Gregorian *et al.*, 2002; Montgomery *et al.*, 2002; Balon, 2006).

However, the double-blind, placebo-controlled trials that assessed SSRI-associated sexual dysfunction by direct questioning consistently found a significantly higher prevalence of sexual dysfunction in the SSRI than in placebo, thereby supporting the proposition that there is a risk of sexual side effects during SSRI treatment (Reimherr *et al.*, 1990; Fava *et al.*, 1998; Coleman *et al.*, 1999, 2001; Croft *et al.*, 1999; Clayton *et al.*, 2006b). The remaining body of nonplacebo-controlled, double-blind comparisons with other antidepressants (Feighner *et al.*, 1991; Feiger *et al.*, 1996; Kavoussi *et al.*, 1997; Segraves *et al.*, 2000; Kennedy *et al.*, 2006) and open-label trials (Modell *et al.*, 1997; Kennedy *et al.*, 2000), also indicate sexual dysfunction as a side effect associated with SSRIs.

In a recent cross-sectional survey in 502 adults in France and the United Kingdom, Williams *et al.* (2006) aimed to establish a more reliable estimate of the prevalence of SSRI- and SNRI-induced sexual dysfunction, by trying to eliminate other causes of sexual dysfunction (e.g., premorbid sexual dysfunction or disease-related sexual dysfunction). Hereto, they only included patients who reached criteria for current sexual dysfunction (total score on Arizona Sexual Experience Scale ≥ 19) and who experienced their sexual function as 'a little' or 'much' worsened compared to before they started antidepressive treatment. This strategy provided prevalence estimates of 39.2% SSRI/SNRI-induced sexual dysfunction in the United Kingdom sample and 26.6% in the French sample.

Most of the studies that focused on SSRI-induced sexual dysfunction, found no significant differences in sexual dysfunction rates between SSRIs. Three of these studies are randomized, double-blind comparisons that provided prevalence rates for sexual dysfunction and levels of significance for this item.

A placebo-controlled comparison of the efficacy and tolerability of paroxetine and fluoxetine was conducted by Fava *et al.* (1998). One hundred twenty-eight outpatients with moderate to severe depression were included and given a 12-week treatment with paroxetine ($N = 55$), fluoxetine ($N = 54$) or placebo ($N = 19$). The paroxetine-treated patients reported significantly more sexual dysfunction (25%) than the fluoxetine (7%)- and placebo (0%)-treated patients ($P < 0.05$). However, the statistical significance disappeared after Bonferroni's correction. Phase-specific sexual functioning was not assessed.

In a non-placebo controlled comparison ($N = 308$), sertraline and citalopram showed no significant differences in prevalence rates of overall sexual dysfunction (men:45% in sertraline and 48.9% in citalopram; women: 23.8% in sertraline and 31% in citalopram), nor in the prevalence rates of phase-specific sexual dysfunction. Sexual side effects were assessed by means of the UKU Side Effect Rating Scale (Ekselius and von Knorring, 2001).

Kiev and Feiger (1997) conducted a non placebo-controlled comparison of fluvoxamine and paroxetine. More than 10% of 60 depressed outpatients reported impotence (21% in paroxetine; 14% in fluvoxamine), ejaculatory abnormality (21% in paroxetine; 7% in fluvoxamine) and libido decrease (17% in paroxetine; 13% in fluvoxamine). These prevalence rates were not significant different for the two SSRIs.

In a large open-label study ($N = 6297$), patients on fluoxetine had a significant lower prevalence of sexual dysfunction (36%) than patients on paroxetine (42%), but this difference was not longer significant when patients with other possible causes of sexual dysfunction were excluded from analysis (23 and 26%, respectively) (Clayton *et al.*, 2002).

Another open-label comparison ($N = 119$) by Landen *et al.* (2005) showed no significant difference in the prevalence of sexual side effects in patients treated with paroxetine (36%) or citalopram (44%), nor in the prevalence of the specific items of sexual functioning.

Finally, an open label study in 107 outpatients found that fluoxetine, paroxetine and sertraline to an equal degree decreased libido (55%), arousal (50%), duration of orgasm (36%) and intensity of orgasm (42%) during treatment (Modell *et al.*, 1997).

Some open-label trials that specifically assessed phase-specific functioning, did report some differences between SSRIs. Montejo-Gonzalez *et al.* (1997), analyzed the incidence rates of SSRI-induced sexual side effects in 344 outpatients. Paroxetine showed the highest incidence rate of overall sexual dysfunction (64.71%), followed by fluvoxamine (58.94%), sertraline (56.4%) and fluoxetine (54.38%), but these differences were not statistically significant. Analysis of phase-specific sexual functioning did show significant differences, with anorgasmia, erectile dysfunction and

decreased vaginal lubrification being more present in patients on paroxetine compared to the other SSRIs ($P < 0.05$).

An extension of this study to a population of 1022 outpatients on antidepressive monotherapy provided similar results. A comparison of the different antidepressants showed the highest incidence-rate in citalopram (72.7%) and paroxetine (70.7%). Sertraline, fluvoxamine and fluoxetine, showed incidence-rates of 62.9, 62.3 and 57.7%, respectively. Again, erectile dysfunction and decreased vaginal lubrification were significantly more associated with paroxetine than with the other SSRIs ($P < 0.005$) (Montejo *et al.*, 2001).

Most authors agree that serotonergic drugs can affect all phases of the sexual response cycle (Montejo-Gonzalez *et al.*, 1997; Segraves, 1998; Rosen *et al.*, 1999; Montejo *et al.*, 2001; Fava and Rankin, 2002; Balon, 2006). In general, delayed ejaculation and orgasm problems are associated more consistently with SSRI-treatment, than libido or arousal problems (Rosen *et al.*, 1999).

Furthermore, some differences in experience of antidepressant-induced sexual side effects are noted between men and women. According to Montejo *et al.* (2001), men experience antidepressant-induced sexual side effects more often than women (62.4% versus 56.9%), while women experience greater severity of symptoms. Clayton *et al.* (2006a), reported that men are more likely to experience impairment of the desire and the orgasm phase compared to women, while they are less likely to experience a dysfunction in the arousal phase.

Interestingly, nearly half of the subjects in a study of Hu *et al.* (2004) qualified SSRI-induced sexual dysfunction as 'a lot' or 'extremely bothersome' and as much as 83.3% of the affected patients still experienced the impairment three months after initiation of therapy. Montejo *et al.* (2001) also assessed tolerance of this adverse event and found that only 24.5% of patients showed good tolerance of sexual dysfunction (i.e., lack of concern despite the presence of sexual dysfunction), while 42.5% were discontent although he/she did not intend to discontinue the treatment for this reason and 32.9% were very concerned about the sexual dysfunction and seriously considered to discontinue the treatment.

In a small sample of psychiatric outpatients ($N = 51$), 27.5% reported that they had actually stopped their psychotropic medication because of sexual side effects (Rosenberg *et al.*, 2003).

Profile of bupropion for sexual side effects To illustrate the profile of bupropion for sexual side effects, we collected information from three sorts of trials.

First, we discuss five randomized, placebo-controlled trials that assessed sexual functioning during bupropion treatment in depressed patients (Coleman *et al.*, 1999, 2001; Croft *et al.*, 1999; Settle *et al.*, 1999; Clayton *et al.*, 2006b). These studies are summarized in Table 1.

In all of these trials, patients were randomly assigned to eight weeks treatment with bupropion, placebo, or an SSRI (except for the first study) after one week placebo lead-in period. All patients scored 18 or more on the 17 or 21-item Hamilton Depression Scale (HAM-D-17 or HAM-D-21).

One study used an open-ended question to assess adverse events and found a <1% prevalence-rate of sexual dysfunction for both the bupropion and placebo-group. The others used a structured interview, based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria of sexual dysfunction disorders, to assess sexual functioning. One study used both the structured interview and the patient-completed Changes in sexual functioning questionnaire (CSFQ).

Looking at the three studies that investigated sexual desire disorder, the prevalence was significantly lower for bupropion than for placebo in one study and comparable in the two other studies.

Looking at the three studies that investigated sexual arousal disorder, no difference in prevalence of sexual arousal disorder was found among treatment-groups of two studies. In the other study significantly more patients on bupropion experienced sexual arousal disorder, compared to placebo. No statistically significant difference for this event was noted between bupropion and sertraline.

Four placebo-controlled studies assessed prevalence of orgasm disorder, showing comparable results for bupropion and placebo and significant better results for bupropion compared to sertraline, fluoxetine or escitalopram.

Looking at the four studies that investigated patient satisfaction with sexual functioning, patients on bupropion and placebo seemed consistently more satisfied than patients on escitalopram, fluoxetine and sertraline.

Furthermore, we found three randomized, double-blind studies (not placebo-controlled) that compared the effect of bupropion and SSRI on sexual functioning (Kavoussi *et al.*, 1997; Segraves *et al.*, 2000; Kennedy *et al.*, 2006). These are summarized in Table 2. The treatment duration in these trials varied from 8 to 16 weeks.

In the first two studies, sexual functioning was assessed by structured interviews, based on DSM-IV criteria of sexual dysfunction disorders. The second study additionally used the Sex Effects Scale (Sex FX scale), a brief 13-item clinician-rated interview that evaluates desire, arousal, orgasm and overall satisfaction with sexual functioning. The third study only assessed orgasm function by an investigator-conducted structured interview.

In all comparisons, bupropion caused less sexual dysfunction than the SSRI. Only in the female subjects of the second study, effects of bupropion and paroxetine were comparable, both resulting in an unchanged sexual function at study-end.

Second, we summarize five clinical trials that investigated the efficacy of bupropion in the treatment of sexual dysfunction in non-depressed patients. Three of these studies have a randomized, double-blind, placebo-controlled design and two studies have a single-blind design.

Crenshaw *et al.* (1987) assessed 30 men and as many women with *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) diagnosis of inhibited sexual desire, inhibited sexual arousal and/or inhibited orgasm. After an eight week washout period with placebo, patients were randomly assigned to 12 weeks of double-blind treatment with bupropion 225–450 mg a day or placebo. Sexual drive and global sexual functioning gradually improved during active treatment and by the end of the trial improvements were significantly greater in the bupropion group. Moreover, 63% of the bupropion-treated patients experienced much to very much global improvement in sexual function after three months of treatment, versus 3% in the placebo-group.

Table 1 Randomized, double-blind, placebo-controlled studies

References	Agents studied	Dose mg/d	N	Duration	Diagnosis	Assessment SF	SF at baseline	SF at endpoint
Settle *et al.* (1999)	placebo bupropion SR	 100–400	385 987	8 weeks	MD (≥20 on HAM-D-17 or HAM-D-21)	Open question	Not assessed	In both groups <1% reported Sexual dysfunction
*Croft *et al.* (1999)	placebo bupropion SR sertraline	 150–400 50–200	121 120 119	8 weeks	MD (≥18 on HAM-D-21)	Structured Interview rating -SDD, SAD, OD, and PE -SF satisfaction	-Normal or SDD -SF variables comparable in all groups	-SDD sign. less in bupropion (19%) versus placebo (31%)**; no sign. difference between sertraline (28%) and bupropion or sertraline and placebo -SAD sign. more in bupropion (6%) and sertraline (12%) versus placebo (1%)**; no sign. difference between bupropion and sertraline -OD sign. less in bupropion (15%) and placebo (9%) versus sertaline (40%)*; no sign. difference between placebo and bupropion -Sign. more patients on placebo (77%) satisfied with SF versus sertraline (65%)**; no sign. difference between placebo and bupropion (75%)
*Coleman *et al.* (1999)	placebo bupropion SR sertraline	 150–400 50–200	124 122 118	8 weeks	MD (≥18 on HAM-D-21)	Structured Interview rating -SDD, SAD, OD, and PE (not reported) -SF satisfaction	-Normal or SDD -SF variables comparable in all groups	-SDD sign. less in bupropion (15%) than in sertraline (30%)**; no sign. difference between placebo (20%) and active treatment -No sign. difference in SAD between bupropion (6%), sertraline (9%) and placebo (10%) -OD sign. less in bupropion (10%) and placebo (14%) versus sertraline (36%)*; no sign. difference between placebo and bupropion -Sign. more patients on placebo (81%) satisfied with SF versus sertraline (62%)**; no sign. difference between placebo and bupropion (75%)

*Coleman *et al.* (2001)	Placebo bupropion SR fluoxetine	 150–400 20–60	152 150 154	8 weeks	MD (≥20 on HAM-D-21)	Structured Interview rating -SDD, SAD, OD -SF satisfaction	-Normal or SDD -less SDD in placebogroup	-SDD sign. less in bupropion (15%) and placebo (13%) versus fluoxetine (24%)**; no sign. difference between bupropion and placebo -No sign. difference in SAD between bupropion (7%), placebo (9%) and fluoxetine (12%) -OD sign. less in bupropion (11%) and placebo (11%) versus fluoxetine (31%)*** -Sign. more patients, who were satisfied with SF at baseline, became dissatisfied while receiving fluoxetine (22%) than patients receiving placebo (9%) or bupropion (3%)**
Clayton *et al.* (2006b)	Placebo bupropion XL escitalopram	 300–450 10–20	273 276 281	8 weeks	MD (≥19 on HAM-D-17)	-Structured Interview rating OD and overall Sexual functioning -CSFQ	-Normal orgasm function -SF variables comparable in all groups	-OD sign. less in bupropion (15%) and placebo (9%) versus escitalopram (30%).; no sign. difference between placebo and bupropion -Overall sexual functioning worsened in sign less with bupropion (20%) and placebo (15%) than with escitalopram (36%) ($P < 0.001$) -CSFQ scores sign. worse in escitalopram versus bupropion**; no sign. difference between placebo and bupropion

SF, sexual function; SR, sustained release; XL, extended release; MD, major depression; HAM-D, Hamilton Depression Scale; SDD, sexual desire disorder; SAR, sexual arousal disorder; OD, orgasmic dysfunction (delay or failure); PE, premature ejacuation; sign., significant; CSFQ, Changes in Sexual Functioning Questionnaire; *$P < 0.001$; **$P < 0.05$; ***$P < 0.01$.

Table 2 Randomized, double-blind studies

References	Agents studied	Dose mg/d	N	Duration	Diagnosis	Assessment SF	SF at baseline	SF at endpoint
Segraves *et al.* (2000)	Bupropion SR Sertraline	100–300 50–200	122 126	16 weeks	Moderate to severe MD	Structured Interview and self-rating -SDD, SAD, OD and PE -SF satisfaction	Normal or SDD, SF variables comparable in both groups	-SDD sign. less in bupropion SR (21%) versus sertraline (34%) ($P = 0.003$) -SAD not sign. different in bupropion (3%) and sertraline (9%) -OD sign. less in bupropion SR (men 7%; women 5%) versus sertraline (men 44%; women 33%)* -Sign. more patients on bupropion (79%) satisfied with SF versus sertraline (58%)*
Kennedy *et al.* (2006)	Bupropion SR Paroxetine	150–300 20–40	141	8 weeks	MD (≥18 on HAM-D-17)	-Sex FX scale -IRSD-F	Lower SF on Sex FX and IRSD-F scales in women	-Sign. deterioration in total Sex FX score***, Desire***, Arousal**, Orgasm*** and Overall Satisfaction*** in men on paroxetine***; no sign. change in scores in men on bupropion -No changes in Sex FX and IRDS-F scores in females of both groups
*Kavoussi *et al.* (1997)	Bupropion SR Sertraline	100–300 50–200	119 122	16 weeks	MD	Structured interview rating orgasm functioning	Normal	-OD sign. less in bupropion (8%) than sertraline (40%)*

SF, sexual function; SR, sustained release; XL, extended release; MD, major depression; HAM-D, Hamilton Depression Scale; SDD, sexual desire disorder; SAR, sexual arousal disorder; OD, orgasmic dysfunction (delay or failure); PE, premature ejacuation; sign., significant; Sex FX scale, Sex Effects Scale; IRSD-F, Investigator-Rated Sexual Desire and Functioning Scale; *$P < 0.001$; **$P < 0.05$; *** $P < 0.01$.

In another placebo-controlled trial, the effect of bupropion on hypoactive sexual desire disorder in 66 premenopausal women was investigated. Bupropion dose varied from 300 to 400 mg/day and sexual functioning was assessed by means of the Changes in CSFQ. The authors found that participants who received bupropion SR scored significantly better on sexual arousal, orgasm completion and sexual satisfaction, but only numerically better on desire scores (Segraves *et al.*, 2004).

In healthy men, no differences were found in self-reported sexual function, number of nocturnal erections, total erection time or penile rigidity in subjects taking bupropion compared with those taking placebo or baseline (Labbate *et al.*, 2001).

Modell *et al.* (2000) studied the effect of bupropion SR on orgasmic delay or inhibition in 30 non-depressed subjects. Patients consecutively received placebo, bupropion SR 150 mg/day and bupropion 300 mg/day, each during three weeks, in a single-blind manner. In women, only orgasm intensity was significantly improved in the bupropion 150 mg/day phase. In men, delay in orgasm/ejaculation and sexual satisfaction improved during placebo-treatment, and these changes became significant during the bupropion 150 mg phase, were they were accompanied by a significant improvement in the ability to have an erection. In both sexes, reported sexual functioning did not differ significantly between the 150/day or 300/day doses.

Another single-blind prospective study studied the profile of bupropion for somatic erectile dysfunction in 14 non-depressed diabetic man. After two weeks of baseline testing, patients received two weeks placebo treatment, followed by bupropion 150 mg t.i.d. during six weeks. Subjective measures of libido, erectile function and sexual satisfaction either remained stable or improved mildly during exposure to bupropion. Physiologic measures like penile brachial index, penile circumference or penile sensitivity showed no overall change under bupropion, while number and duration of nocturnal 'erectile episodes' did increase significantly in the bupropion group compared to placebo (Rowland *et al.*, 1997).

Third, we mention three small open-label studies that assessed the effect of a switch to bupropion on SSRI-induced sexual side effects. Dobkin *et al.* (2006) switched 18 depressed women with low sexual desire, together with poor tolerability and/or efficacy of their ongoing SSRI-treatment to bupropion. Two weeks after the switch, significant improvements in desire were noted, while arousal and orgasm clearly improved after four weeks of treatment.

Another open-label study ($N = 11$) showed comparable results. Depressed patients treated with an SSRI, were assessed during SSRI therapy, after two weeks of combined treatment of the SSRI and bupropion, after tapering the SSRI and during bupropion monotherapy. Sexual functioning improved clearly after introduction of bupropion and continued to improve on bupropion monotherapy (Clayton *et al.*, 2001).

Finally, Walker *et al.* (1993) investigated the sexual functioning of 31 patients, who developed anorgasmia or orgasm dysfunction while receiving fluoxetine treatment for depression. At the end of a two-week wash out period, four patients (13%) reported a return to normal orgasm function. This number increased to 84% after eight weeks of bupropion treatment. Furthermore, 81% of patients reported 'much' to 'very much' improvement in libido and satisfaction with overall sexual functioning at the end of the study.

Can bupropion reverse SSRI-induced sexual dysfunction?

Bupropion-addition is, according to Dording *et al.* (2002), the strategy most frequently used by clinicians in the management of SSRI-induced sexual side effects.

Medline searches revealed three randomized, double-blind, placebo-controlled studies and four publications of open trials assessing the effect of bupropion-addition in SSRI-associated sexual dysfunction.

Masand *et al.* (2001) compared bupropion 150 mg/day with placebo for SSRI-induced sexual dysfunction in 30 euthymic adults during a 3-week randomized, double-blind, placebo-controlled trial. At study end, the mean improvement on the Arizona Sexual Experiences Scale (ASEX) was about 25% and not significantly different in placebo and bupropion patients.

In a similar study, 41 patients (24 women and 17 men) with SSRI-induced sexual side effects completed a 6-week trial with bupropion SR or placebo in addition to their current treatment. During this trial, patients also used a fixed morning dose of 150 mg bupropion a day. Sexual functioning was also measured by the ASEX, together with the Brief Index of Sexual Functioning. At the end of the trial no significant differences were seen between placebo and bupropion SR on any measure of sexual functioning (DeBattista *et al.*, 2005).

Clayton *et al.* (2004) also compared bupropion SR with placebo in 42 (37 women and 5 men) depressed patients with SSRI-induced sexual dysfunction in another randomized, double-blind, placebo-controlled study. These patients all experienced global or phase-specific sexual problems, while responding to an ongoing SSRI treatment. During four weeks, bupropion SR 150 mg b.i.d. was added to their current antidepressant. On the CSFQ, patients of the bupropion-group showed a significantly greater improvement in frequency of sexual activity compared with those receiving placebo. However, no differences were found for global sexual functioning, arousal, orgasm and interest in sexual thoughts or fantasies.

In a small open label study, Labbate *et al.* (1997) added 75 mg of bupropion to an ongoing SSRI treatment in eight patients who had experienced a decline in sexual function since the start of the SSRI. After four weeks of bupropion treatment, 50% of the participants rated their global sexual function as much improved. Remarkably, all of the responders were women. No participant experienced worsened sexual function and all eight patients tolerated the combination of agents, except for one woman, who reported spontaneous orgasm.

Ashton and Rosen (1998) investigated the efficacy of bupropion as an antidote for SSRI-induced sexual dysfunction in 47 psychiatric outpatients. Bupropion was added to their current antidepressant, either as a p.r.n. dose of 75 or 150 mg one or two hours before sexual activity or as fixed dose of 75 mg t.i.d. Overall, 66% of the participants reported a reduction of sexual dysfunction. Improvement was seen in all phases of the sexual response cycle, with a trend toward greater improvement in desire and orgasm phases. Seven of 47 patients discontinuated bupropion addition, because of adverse effects like anxiety and tremor.

Another open label study investigated the effect of combining bupropion SR with venlafaxine, paroxetine or fluoxetine, in 19 patients with treatment-induced sexual dysfunction. After at least

six weeks treatment with SSRI/SNRI monotherapy, 150 mg bupropion/day was added during eight weeks. Numeric improvement occurred in all three domains of sexual function (desire, arousal and orgasm) after eight weeks of combination treatment, but these differences were statistically significant only for orgasm in women and for global sexual functioning in men (Kennedy *et al.*, 2002).

Finally, Gitlin *et al.* (2002) evaluated 24 patients (15 women and 9 men) with SSRI-induced sexual side effects, during a seven-week combination treatment with bupropion. During the first week bupropion 100 mg was added to the SSRI. If necessary, bupropion dose was increased with 100 mg a week, to maximum 300 mg/day. Bupropion addition resulted in improvement of all sexual side effects in both men and women. More than 50% of the improvement occurred within the first two weeks and at low dose (100–200 mg/day). Three subjects dropped out of the study within two weeks because of intolerance to stimulating side effects of bupropion.

Weight gain

Prevalence of SSRI-induced weight gain

Data on the long-term effects of SSRI on body weight are scarce. We found one randomized, double-blind, placebo-controlled study in which the changes in weight during continuation treatment with fluoxetine were explored. Three-hundred and ninety five depressive patients in remission after 12 weeks of acute fluoxetine treatment, were randomly assigned to a continuation therapy up to 38 weeks with either placebo or fluoxetine 20 mg/day. Changes in weight during acute and continuation treatment were analyzed and relationships between weight change, body mass index and appetite change were assessed. During acute treatment, there was a small but significant decrease in weight for all patients. Most of this weight loss occurred during the first four weeks of therapy. During continuation treatment, all participants (fluoxetine- and placebo-group) showed a significant weight gain. Mean absolute weight increase was 1.1 kg at week 26, 2.2 kg at week 38 and 3.1 kg at week 50. Fluoxetine-treated patients had gained slightly less weight at week 26 compared to the placebo-group, but this difference disappeared in week 38 and 50. Weight increase was not related to body mass index at baseline, but was positively related to poor appetite at study entry and to improvement in appetite after recovery (Michelson *et al.*, 1999).

In a randomized, double-blind trial, Fava (2000) examined the differential effects of fluoxetine, sertraline and paroxetine on body weight during long-term treatment. After a placebo-lead in period, 284 patients with major depressive disorder received one of three agents for a treatment period of 26–32 weeks. Mean percent change in weight and number of patients who gained ≥7% weight were compared among the patients who completed 26–32 weeks of therapy (fluoxetine $N = 44$, sertraline $N = 48$, paroxetine $N = 47$). Weight gain during continuation treatment differed between the SSRIs. From baseline to endpoint, fluoxetine patients showed a small mean decrease in weight (–0.2%) and sertraline patients showed a small mean increase (1.0%). These weight changes were not statistically significant compared to baseline or each other. However, patients from the paroxetine-group did show a significant increase in weight (3.6%) and a significantly higher proportion of them gained ≥7% weight compared with sertraline and fluoxetine groups. The author marks that this differential effect does not support the opinion that weight-gain during antidepressive therapy is the result of remission of symptoms.

A similar differential effect was also seen during long-term serotonin reuptake inhibitor treatment in patients with obsessive compulsive disorder. In a naturalistic, prospective trial, all five SSRIs and clomipramine were examined during 2.5 year treatment of 138 OCD patients. At the end of the trial, patients had gained a mean of 2.5% of their initial body weight (statistically significant; $P < 0.001$) and in 14% of them, weight increased by more than 7%. The proportion of patients with a >7% weight increase was 4.5 and 8.7% for sertraline and fluoxetine respectively, 14.3, 10.7 and 14.3% for citalopram, fluvoxamine and paroxetine respectively and 34.8% for clomipramine (Maina *et al.*, 2004).

Profile of bupropion for weight gain

Again, we first explore what is known about the effect of bupropion on body weight in depressive patients. A study of Harto-Truax *et al.* (1983) is one of the early reports that focused on this matter. The authors collected the results of open, comparative and placebo-controlled trials and concluded that bupropion was not associated with significant weight gain, appetite change or changes in caloric intake.

More recently, three randomized, double-blind, placebo-controlled studies assessed body weight during eight weeks of bupropion treatment in patients with major depression.

Settle *et al.* (1999) pooled data from three similar trials, including 987 subjects treated with bupropion SR 100–400 mg/day and 385 subjects on placebo. From baseline to study-end, bupropion SR-treated patients experienced weight loss in a dose-related manner. A daily dose of 100 mg/day was associated with a mean weight loss of 0.4 kg, 300 mg/day with a mean weight loss of 0.9 kg and 400 mg/day with a mean weight loss of 1.3 kg. In the placebo-group no weight change was observed.

A comparable dose-related weight loss was reported by Reimherr *et al.* (1998). They assessed changes in body weight in three treatment groups: bupropion SR 150 mg/day ($N = 121$), bupropion SR 300 mg/day ($N = 120$) and placebo ($N = 121$). Between baseline and discontinuation, the placebo-group experienced a weight loss of 0.2 kg, while patients on bupropion 300 and 150 mg/day showed a mean weight loss of 1 and 0.5 kg respectively. For both bupropion-groups, mean weight change differed already significantly from placebo at day 7.

These results are confirmed in a third trial ($N = 139$). During eight weeks treatment with bupropion XL 300–450 mg /day, patients lost a mean of 1.1 kg, compared to 0.2 kg in placebo (Jefferson *et al.*, 2006).

One randomized placebo-controlled study investigated the long-term effects of bupropion SR on body weight in patients with major depression. During an open trial of eight weeks, patients were treated with 300 mg bupropion SR. Afterwards, responders were randomly assigned to a double-blind bupropion 300 mg ($N = 210$)

or placebo regimen ($N = 213$) during another 44 weeks. During the open-label phase, patients lost an average of 1.4 kg. This weight loss was maintained during the double-blind treatment with bupropion, while weight returned to baseline during double-blind treatment with placebo (–1.15 kg and +0.2 kg weight change from baseline to the study-end in the bupropion and placebo groups, respectively). Remarkably, weight loss was greater in patients with higher BMI at baseline (Croft *et al.*, 2002).

Furthermore, some randomized, double-blind studies compared the effect of bupropion and SSRIs on body weight. In tables 1 and 2, the four studies indicated with an asterisk reported the mean change in weight in the bupropion and SSRI groups (Kavoussi *et al.*, 1997; Coleman *et al.*, 1999, 2001; Croft *et al.*, 1999). In each of these studies, there was a small weight decrease in all patients. Patients on bupropion lost more weight than those on SSRIs, but this difference was not significant.

Second, some authors investigated whether bupropion would be useful in the management of obesity in non-depressed patients. Gadde *et al.* (2001) conducted the first randomized, double-blind, placebo-controlled trial in 50 overweight and obese women (BMI > 27) without symptoms of depression. After eight weeks of double-blind treatment with placebo or bupropion to a maximum of 400 mg/day, non-responders (lost < 5% of body weight) were switched to the other treatment-arm, while responders continued the same treatment to a total of 24 weeks. All participants were instructed to follow a 1600 kcal/d diet during the trial. After eight weeks, the 18 patients who completed bupropion therapy lost an average of 6.4 kg of body weight, compared with an average of 1.5 kg in the 13 patients on placebo ($P = 0.0001$). Sixteen responders (14 on bupropion and 2 on placebo) completed the continuation phase. After 24 weeks, completers in the bupropion-group had a mean weight loss of 12.5 kg, while completers in the placebo group lost 10.7 and 10.4% of their initial body weight.

In another double-blind, placebo-controlled study of 26 weeks also a significant effect of bupropion (300–400 mg/day) on body weight is seen in 229 obese patients (BMI 30–44 kg/m^2) with depressive symptoms (but not meeting criteria for major depression). All included patients were prescribed to a mild hypocaloric diet (500 kcal deficit/day). After 24 weeks, completers on bupropion lost significantly more weight and reported significantly less craving and hunger than patients on placebo (Jain *et al.*, 2002).

A more extended placebo-controlled, double-blind study was conducted by Anderson *et al.* (2002). Two-hundred and twenty seven obese men and women (BMI 30–44 kg/m^2) completed 24 weeks of treatment with either bupropion SR 300 mg/day, bupropion SR 400 mg/day or placebo, in combination with energy-restricted diets, meal replacements and exercise. At the end of these first 24 weeks, mean loss of initial body weight was 5.0, 7.2 and 10.1% subjects on placebo, bupropion 300 mg/day and bupropion 400 mg/day, respectively (differences are statistically significant). After week 24, placebo-subjects were randomly assigned to a double-blind treatment with 300 or 400 mg bupropion/day for another 24 weeks, while bupropion-subjects continued their treatment . In the initial placebo group, weight loss increased to 6.4% after 24 weeks of bupropion 300 mg/day treatment and to a loss of 7.2% after 24 weeks of bupropion 400 mg/day. In both bupropion groups, no significant changes in weight were noted during the continuation phase.

Moreover, all three studies reported that significantly more patients in the bupropion group lost at least 5% of their initial body weight compared to the placebo group.

Can bupropion reverse SSRI-induced weight gain? Several strategies, like nutritional counselling, physical exercise, switch to other antidepressant with a lower risk for weight gain or addition, are suggested in the management of SSRI-induced weight gain. Of these, switching agents is described as the most preferred option for the majority of psychiatrists (93%) (Dording *et al.*, 2002). Addition of certain agents, such as ephedrine, sibutramine, naltrexone, histamine H2 receptor antagonists, topiramate or bupropion, is a less popular strategy. This probably reflects the fact that there is only anecdotal evidence for this practice and that none of these agents, including bupropion, has been systematically assessed as add-on therapy in SSRI-induced weight gain (Fava, 2000; Dording *et al.*, 2002; Masand and Gupta, 2002).

We found one small study that did examine the effect of bupropion add-on therapy, not in antidepressant-induced, but in olanzapine-induced weight gain. Eight patients who gained a mean of 13.3 kg during at least 12 weeks of olanzapine treatment were included. During 24 weeks bupropion (300 mg/day in seven patients, 150 mg/day in one) was added to the ongoing olanzapine therapy, together with nutritional counselling. Mean bodyweight decreased only marginally, although significantly over time (99.6–96.2 kg, $P < 0.001$). However, these results should be interpreted with caution, because of the small study sample and lack of a control group (Gadde *et al.*, 2006).

Emotional detachment

Prevalence of SSRI-induced 'emotional detachment'

The concept of emotional detachment in SSRI treatment was brought under the attention by a series of case-reports (Hoehn-Saric *et al.*, 1990; Oleshansky and Labbate, 1996; Garland and Baerg, 2001; Reinblatt and Riddle, 2006) and a small open-label study conducted by Opbroek *et al.* (2002).

At present, however, the exact definition of emotional detachment is far from clear.

First, the lack of an adequate definition is reflected in the diversity of reported terms and in the fact that these terms are often used interchangeably, while it is not clear how these terms relate to each other. Opbroek *et al.* (2002) for example reported on emotional detachment, Reinblatt and Riddle (2006) on a lack of motivation, Garland and Baerg (2001) on unconcern, apathy and emotional disconnection and Hoehn-Saric on apathy, indifference and lack of motivation. The fact that it is unclear whether the concept mainly points to emotional or motivational symptoms, is illustrated by the study from Opbroek *et al.* (2002) in which emotional blunting was measured by a self-report scale that not only assesses the ability of patients to feel different emotions, but also the ability to feel motivated or to feel energetic.

Second, it is difficult to distinguish whether emotional blunting or apathy are part of the depressive episode, are treatment induced, residual symptoms (i.e., core depressive symptoms that have not resolved with treatment), personality traits, or a combination of these factors (Balon, 2002; Fava, 2003, 2006; Menza *et al.*, 2003). Fava (2003) investigated the prevalence of cognitive and physical symptoms during long-term antidepressant treatment, and suggested that apathy is likely to be both a side effect of antidepressants as well as a residual symptoms of depression.

Third, the paucity of data does not allow to conclude whether emotional blunting is specific to serotonergic agents, as there are no data available on emotional blunting for non-serotonergic antidepressants.

Apart from the conceptual problems outlined above, the limited amount of literature makes it impossible to provide prevalence figures on emotional detachment during SSRI treatment.

In general, the existing case reports concerning SSRI-induced emotional detachment, describe dose-related and reversible decreases in motivation and emotional responsivity, different from a sense of sedation or symptoms of depression (Hoehn-Saric *et al.*, 1990; Garland and Baerg, 2001; Marangell *et al.*, 2002; Reinblatt and Riddle, 2006). Dose reduction, evening dosing, augmentation and switching agents are suggested management strategies of SSRI-associated emotional detachment. Again, these strategies are only supported by anecdotical reports (Hoehn-Saric *et al.*, 1990; Oleshansky and Labbate, 1996; Garland and Baerg, 2001; Corcoran *et al.*, 2004; Reinblatt and Riddle, 2006).

Profile of Bupropion for 'emotional detachment'

To the best of our knowledge, no trials are published that investigated the profile of bupropion for emotional blunting or apathy. Only some case-reports by Marin *et al.* (1995) and Corcoran *et al.* (2004), suggested that some patients presenting with apathy during organic brain disease or depression had beneficial effects of a treatment with bupropion.

The available papers mainly focus on the profile of bupropion for symptoms like fatigue and sleepiness. We preferred to distinguish between trials that investigated the profile of bupropion for fatigue and sleepiness as symptoms of depression, for these symptoms as a side effect, and for sleepiness and fatigue as residual symptoms.

First, the profile of bupropion and SSRIs for fatigue and sleepiness as symptoms of depression was explored by Papakostas *et al.* (2006), analyzing data from six double-blind, randomized clinical trials. The authors used changes in scores of HAM-D items on sleepiness and fatigue to assess improvement in 662 patients on bupropion; 655 patients on SSRIs and 489 on placebo. Controlling for baseline scores, there was a greater improvement in hypersomnia and fatigue in the bupropiongroup, than in the SSRI- ($P < 0.001$ and $P = 0.0078$) and placebo-group ($P = 0.008$ and $P < 0.001$). Another study by Jamerson *et al.* (2003) assessed the effect of bupropion on specific symptom clusters of depression in 910 psychiatric outpatients. The authors combined fatigue and interest in one symptom cluster, based on principal component analysis on the 31 item HAM-D. Included patients all participated in eight-week, multicenter, randomized, double-blind, placebo-controlled trials comparing bupropion ($N = 527$) with placebo ($N = 383$). Patients on bupropion showed a significant reduction in 4 symptom clusters compared to placebo, including the fatigue/interest cluster ($P = 0.003$).

Second, the profile of bupropion for side effects as fatigue and sleepiness is suggested to be rather favourable by a number of authors (Stahl *et al.*, 2003, 2004; Fava *et al.*, 2005; Baldwin and Papakostas, 2006). This suggestion is supported by several double-blind studies that reported on this side effect.

In a double-blind, placebo-controlled trial by Croft *et al.* (1999) ($N = 360$), bupropion showed significantly smaller somnolence rates than sertraline (3% versus 17%; $P < 0.05$) and showed comparable somnolence rates to placebo (6%). A non placebo-controlled trial by Kavoussi *et al.* (1997) found comparable results (2% somnolence in bupropion versus 13% in sertraline; $P < 0.05$). Another double-blind study with sertraline as the SSRI-comparator did not provide exact somnolence rates, since side effects with a low prevalence were excluded from analysis. A low prevalence was defined as a rate of less than 10% in any treatment group (Coleman *et al.*, 1999).

The safety profile of bupropion was also compared with fluoxetine in a placebo-controlled trial ($N = 456$). Again, bupropion showed lower somnolence rates than the SSRI (3% versus 11%) and showed comparable somnolence rates to placebo (4%). Levels of significance were not provided (Coleman *et al.*, 2001).

A smaller study ($N = 100$) compared the efficacy and safety of bupropion and paroxetine in elderly depressed patients, showing that 6% of patients experienced somnolence during bupropion treatment versus 27% during paroxetine treatment ($P < 0.05$) (Weihs *et al.*, 2000).

Three placebo-controlled trials without SSRI-comparator did not provide exact somnolence rates, again because of the low prevalence in both the bupropion- and the placebo-group. In two of these trails, the prevalence of somnolence was less than 5% in both groups (Settle *et al.*, 1999; Weihs *et al.*, 2002) in the other trial less than 10% (Reimherr *et al.*, 1998).

Additionally we mention that in three of the five double-blind comparisons, the rate of insomnia as a side effect of bupropion treatment was not higher in bupropion than in the SSRI comparator. In the two trials by Coleman et al. however, there was more insomnia in the bupropion-group (14% in bupropion versus 10% in fluoxetine and 20% in bupropion versus 17% in sertraline respectively; no levels of significance provided) (Coleman *et al.*, 1999, 2001). In one placebo-controlled study without SSRI comparator, insomnia was more prevalent in bupropion (10.5% versus 6.5%; $P < 0.05$) (Settle *et al.*, 1999); in the second insomnia rates were comparable for bupropion and placebo (both 3%) (Weihs *et al.*, 2002) and in the third, insomnia occurred in less than 10% of patients in both groups (Reimherr *et al.*, 1998).

Finally, the profile of bupropion for fatigue and sleepiness as residual symptoms was assessed in the aforementioned trial of Papakostas *et al.* (2006). Among the participants who reached remission at end point (HDRS-17 score ≤ 7) there were significantly fewer patients in the bupropion-group who experienced residual hypersomnia (20.5% versus 32.1%; $P = 0.0014$) or fatigue than patients in the SSRI-group (19.5% versus 30.2%; $P = 0.0020$).

Can bupropion reverse SSRI-induced 'emotional detachment'?

Again, we are not aware of trials that explored the efficacy of bupropion-addition on emotional detachment or apathy during SSRI-treatment.

There is one case-report suggesting that bupropion could be effective as add-on therapy in apathy associated with SSRI treatment. In this report, a 17-year old girl is described with chronic symptoms of mild major depression with irritability and affective instability. Her symptoms clearly improved with fluoxetine 20 mg and remitted further on doses until 40 mg. After this dose-increase, however, she presented with a flattened affect and she seemed unmotivated for school and sports. While dose reduction of fluoxetine was insufficient to relieve these symptoms, addition of bupropion 150 mg/day led to normalisation of affect and motivation (Garland and Baerg, 2001).

Green (1997) presented three additional cases in which patients during treatment with fluoxetine or paroxetine experienced fatigue, whether or not in combination with lack of motivation. As in the previous report, their fatigue or a motivation improved shortly after addition of bupropion.

Conclusion

The present paper explores the profile of SSRIs and bupropion for sexual side effects, weight gain and 'emotional detachment' and examines the available evidence for bupropion-addition in the management of these adverse events when induced by SSRIs.

First, there is robust evidence that SSRIs can induce sexual side effects, and that bupropion causes less sexual dysfunction than SSRIs. Reversal of SSRI-induced side effects by bupropion-addition is supported by limited, mainly open-label evidence.

Second, there is good evidence that long-term treatment with some SSRIs, for example, paroxetine, can result in weight gain, and that long-term treatment with bupropion can result in a small weight loss. Reversal of SSRI-induced weight gain by bupropion addition is supported only by anecdotical evidence.

Third, there is some evidence that SSRIs can induce emotional detachment, apathy or fatigue. Bupropion, on the other hand, seems to be effective on the depressive symptom cluster of fatigue, energy and hypersomnia and seems to induce these side effects less often than SSRIs. No data are available on the reversal of SSRI-induced emotional detachment by bupropion-addition.

Conflicts of interest statement

Koen Demyttenaere acts as a consultant to Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Lundbeck, Wyeth; holds a research grant from Eli Lilly and from GSK, and has accepted paid speaking engagements in industry supported symposia from Boehringer Ingelheim, Eli Lilly, GSK, Lundbeck, Organon, Solvay and Wyeth.

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