Tolerability and profile of the side effects of bupropion

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Tolerability and the profile of side effects of bupropion are reviewed based on the current literature with special emphasis on sexual function and body weight. Clear evidence exists that bupropion causes less sexual dysfunction than SSRIs and more limited evidence that bupropion may reverse the secondary sexual effects of the SSRIs. On the other hand, contrasted evidence is found that long-term treatment with SSRI may entail some weight gain, while long term treatment with bupropion may entail mild weight loss. Currently, sufficient scientific evidence does not exist to state that bupropion can reverse SSRI-induced weight gain.

The results of the review are compared with the opinion of professionals who manage the drug in the daily clinical practice.

INTRODUCTION

A review of the most relevant articles of both original studies as well as reviews, including meta-analysis of the many studies published on the tolerability and side effects of bupropion, has been carried out. The data bases on the safety of bupropion include thousands of participants in clinical trials and more than 40 million patients who have received the drug in the clinical practice.[1]

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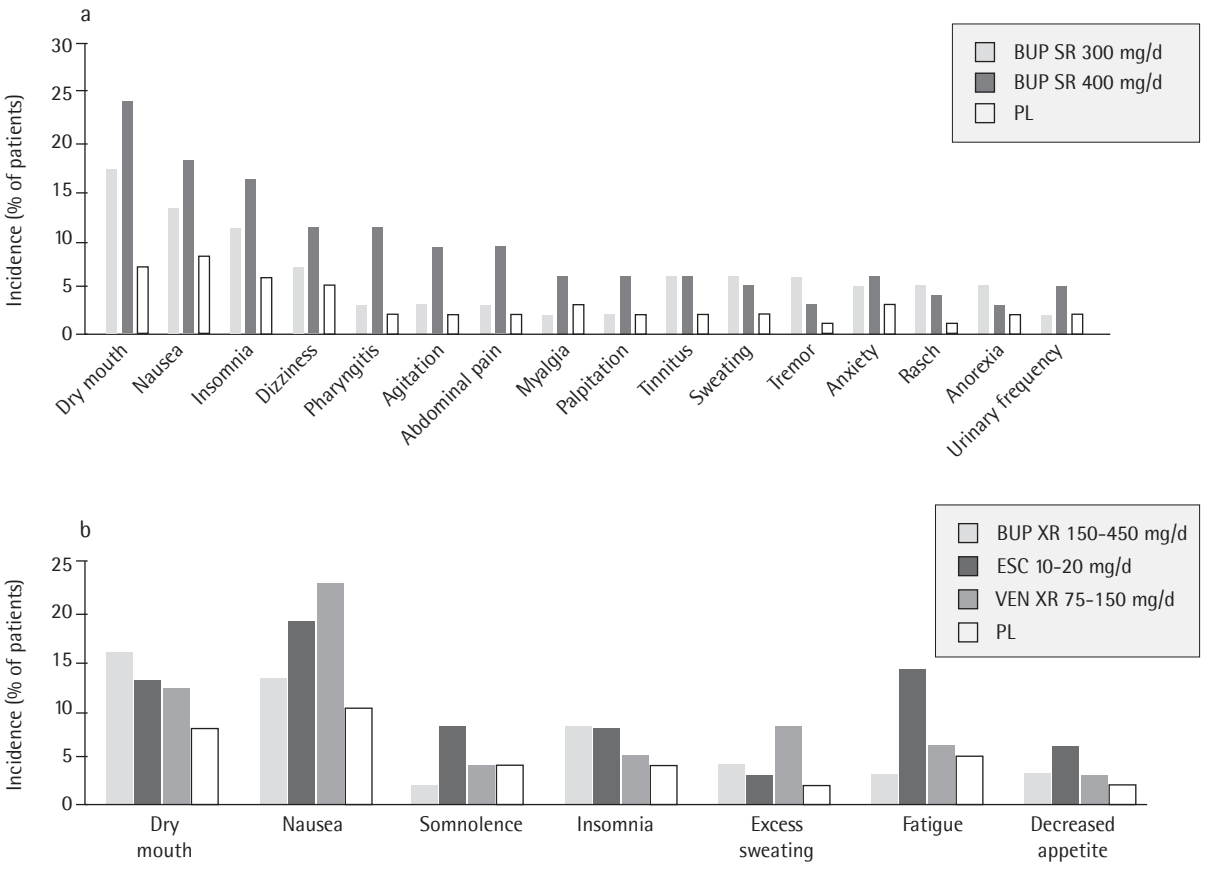
General tolerability profile of bupropion

The profile of side effects of bupropion responds to its particular action mechanism capable of potentiating monoaminergic neurotransmission thanks to a dual effect on the norepinephrine and dopamine reuptake inhibition, with almost no serotoninergic activity since it has a practically null effect on the serotonin transporter. It also lacks significant effects on the histaminergic, muscarinic, alfa-adrenergic or dopaminergic receptors.

In one work that included three studies comparing bupropion SR and placebo, Settle et al.[2] found that the adverse events reported most frequently (with and incidence superior to 5% and greater than that with the placebo) were headache, mouth dryness, nauseous, insomnia, constipation and dizziness. Of these, there was a statistically greater incidence of mouth dryness, nausea and insomnia with bupropion SR than with placebo.

The adverse events rate motivating treatment discontinuation was 7% in all of the dose groups (9% and 11% with 300 and 400 mg/day of bupropion SR, respectively), in comparison with 4% with placebo. The adverse events reported most frequently and that motivated discontinuation of bupropion SR in these trials were exanthema, nausea, agitation and migraine. Bupropion SR is also well tolerated in the long term. In a 52-week long study by Weihs [3] on prevention of relapses, the adverse events were less frequent in the randomized part of the study (9% in the open phase *vs* 4% in the double-blind phase, after the 12th week). This indicates that the adverse events can be decreased with treatment and maintenance.

Agitation was also a common adverse event, it being reported more frequently than with the placebo for the immediate-release bupropion formulation.[4]



Tolerability profile of bupropion sustained release (BUP SR) and bupropion extended/modified release (BUPO XR) in patients with major depressive disorder (MDD). Pooled incidences of treatment-emergent adverse eventes (a) occurring in ≥ 5% of bupropion SR recipients and with a frequency twice that of placebo (PL) in patients receiving BUP SR 300 or 400 mg/d (n=376 or 114) or PL (n=385) in clinical trials (duration of treatment not reported; clinical trials and the age of patients not identified); and (b) ocurring in >5% of patients in any treatment gorup and with a frequency twice that of PL in patients receiving BUP XR 150-450 mg/d (n=801), escitalopram (ESC) 10-20 mg/d (n=281), venlafaxine extended release (VEN XR) 75-150 mg/d (n=385) or PL (n=796) for 8 weeks in four active and one placebo-controlled trial in adults with moderate to severe MDD.

Figure 1 | Dhillon el al. 2006

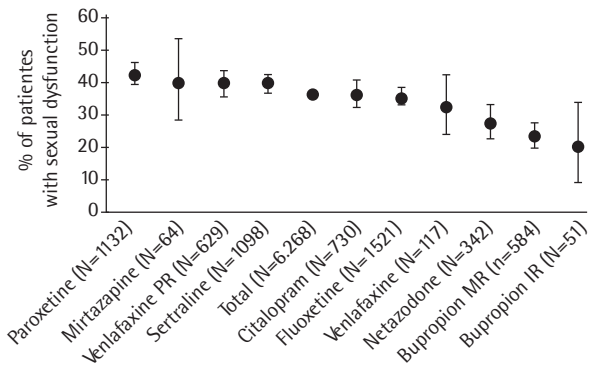
Appearance of seizures may also be an important adverse event. Its incidence is 0.4% (1/1000) with the SR formulation at a dosage of 300 mg/day. This incidence is similar to that seen with the SSRIs. Given that some factors may increase the risk of seizures, the presence of coexisting diseases or concomitant drugs that may decrease the seizure threshold should be ruled out.[1]

The possibility of allergic or anaphylactic reactions has been rarely described and should naturally require treatment suspension.

Bupropion has not shown significant effects on blood pressure or heart rate in placebo-controlled studies.[2] However, in one study in which bupropion was combined with a nicotine patch, one case of treatment-emergent hypertension in the combination group was recorded. Therefore blood pressure should be monitored in patients treated with bupropion in combination with a nicotine patch.[1]

The incidence of insomnia with bupropion (11%–20%), although greater than with placebo (4%–7%), is similar to that associated to SSRI (10%–19%),[5] while the incidence of somnolence with bupropion is similar to that of the placebo and inferior to that reported with SSRI, tricyclic antidepressants and trazodone.

Although the effects of bupropion on the risk of suicide are not clear, it is recommended that the patients be carefully monitored.[4]



[a]Sexual dysfunction is defined by a score on the Changes in Sexual Functioning. Questionnaire based on sexual function equal to or less than the total specific threshold score for each gender. The bars represent the 95% confidence interval.
Abbreviations: IR = immediate-relesase. MR = maintained-release. PR = prolonged-release

Figure 2 Prevalence of sexual dysfunction. Total clinical population[a]

PROFILE OF BUPROPION REGARDING SEXUAL FUNCTION

A common adverse effect in the treatment with SSRI is sexual dysfunction, that can reach rates of up to 80% according to some studies[6] and that is a frequent cause of treatment drop-out.

The profile of bupropion regarding the sexual function and dysfunction can be illustrated from three interesting points of view:

- Comparison of bupropion with placebo or SSRI.
- Switching to bupropion from an SSRI.
- Use of bupropion to treat SSRI-induced dysfunction.

Comparison of bupropion with placebo or SSRI

In all the studies that have compared SSRI and bupropion, there was less sexual dysfunction with bupropion than the SSRIs.

Thase et al.[7] conducted an analysis of the comparison studies of bupropion with SSRI. Bupropion SR caused less orgasmic dysfunction and reduced arousal and sexual desire less than the SSRIs. In this extensive data group, the risk of sexual dysfunction during treatment with bupropion was almost identical to that found with the placebo.

Clayton et al.[8] carried out an extensive observational and cross-sectional study with 6,297 patients who received antidepressants in monotherapy. They compared bupropion with the newer antidepressant available when the trial was performed, that is citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine and venlafaxine XR. The prevalence of sexual dysfunction was measured with the Changes in Sexual Functioning Questionnaire. The use of immediate-release bupropion (IR) (22%), modified-release (MR) (25%) and nefazodone (28%) was associated to a lower risk of sexual dysfunction while selective serotonin reuptake inhibitors (SSRI), mirtazapine and prolonged -release (PR) venlafaxine were associated to higher rates (36%-43%). In one subpopulation of the study with few predisposing factors of sexual dysfunction, the prevalence of said dysfunction varied from 7% to 30%, the likelihood of having sexual dysfunction being 4 to 6 times greater with the SSRIs or with venlafaxine prolonged -release (PR) than with bupropion modified-release (MR) (Table 2). On the other hand, the authors stress the fact that the physicians consistently underestimated the prevalence of antidepressant-associated sexual dysfunction.

Demyttenaere and Jaspers[9] collected five randomized and placebo controlled trials that evaluated sexual function during treatment with bupropion in depressed patients.[2,5,10-12]

In the five studies, the patients were randomly assigned to eight weeks of treatment with bupropion, placebo or an SSRI. All the patients scored 18 or more on the Hamilton depression rating scale.

One study used an open questionnaire to evaluate the adverse effects and found a rate of less than 1% of sexual dysfunction for both bupropion and the placebo group. The other studies used a structured interview based on the DSM-IV sexual dysfunction criteria. One study used both the structured interview and the Changes in Sexual Functioning Questionnaire (CSFQ).

Of the three studies that investigated the sexual desire disorder, two found a prevalence equal to that of the placebo while in the other, the prevalence was significantly less for bupropion than for the placebo.

Three studies investigated the sexual arousal disorder. In two of them, no differences were found between the different treatment groups, while in the other, a significantly greater number of patients with bupropion experienced a sexual arousal disorder compared to the placebo group.

Four studies evaluated the prevalence of orgasmic disorder, showing comparable results between bupropion and placebo and significantly greater results for bupropion compared with sertraline, fluoxetine or escitalopram.

Similar results were obtained in the four studies investigating degree of satisfaction with sexual functioning. The patients with bupropion and placebo were consistently

more satisfied than the patients taking escitalopram, fluoxetine and sertraline.

The authors found three other studies that made a double-blind comparison without placebo of the effect of bupropion and several SSRIs on sexual function.[13-15] In all the comparisons, bupropion caused less sexual dysfunction than the SSRIs, except in the Kennedy et al. study [15] in which significant differences were only found in favor of bupropion in masculine sexual function while for women, the effects of bupropion and paroxetine were comparable. Neither paroxetine nor bupropion were able to improve the low sexual function characteristics of the depressive state.

Switching to bupropion from an SSRI

Three open studies evaluated the effect of a switch to bupropion due to the SSRI induced sexual side effects.

Walker et al.[16] investigated sexual functioning of 31 patients who developed orgasmic dysfunction while being treated with fluoxetine for depression. After a 2-week washout period, four patients (13%) reported recovery of the orgasmic function. This number increased up to 84% after eight weeks of treatment with bupropion. A total of 81% of patients reported "improvement or much improvement" in desire, and satisfaction with the sexual function in general at the end of the study.

Dobkin et al.[17] switched 18 depressed women belonging to minority ethnic groups with low sexual desire due to their treatment with SSRIs (150-300 mg/day) to bupropion. Two weeks after the change, significant improvements occurred in desire, while arousal and orgasm clearly improved after 4 weeks of treatment.

Another small open study [18] showed similar results. Eleven depressed patients treated with an SSRI were evaluated during treatment with the SSRI, after 2 weeks of combined treatment with SSRI and bupropion, after decreasing the SSRI and during the monotherapy with bupropion. Sexual functioning improved clearly and continued improving in the monotherapy with bupropion.

Use of bupropion to treat SSRI induced dysfunction

Adding bupropion to treatment with SSRI is one of the strategies used most in the management of SSRI induced sexual adverse effects. In the studies that have evaluated this possibility, bupropion was added to SSRI or to SNRI as a daily regime, since there are no data supporting the use of bupropion on demand. Furthermore, given its pharmacokinetics and pharmacodynamics, this type of administration would not be adequate.[1]

Demyttenaere and Jasper[9] found three randomized double-blind placebo-controlled studies and for open studies that evaluated the effect of adding bupropion to treatment with an SSRI associated to sexual dysfunction.

Two of the three open studies could not demonstrate significant improvement in the bupropion treated group: Masand el al.[19] compared bupropion, 150 mg/day with placebo in SSRI induced sexual dysfunction and 30 patients during a three-week period. At the end of the study, the improvement in the Arizona Sexual Experience Scale (ASEX) was 25% and this did not differ significantly between patients with placebo and bupropion.

In a similar study, [20] 41 patients (24 women and 17 men) with SSRI-induced sexual side effects completed a six-week trial with bupropion SR or placebo, added to their usual treatment. During this trial, the patients also took a dose of 150 mg/day of bupropion and sexual functioning was measured with the ASEX scale and the Brief Index of Sexual Functioning. At the end of the study, no significant differences were found between placebo and bupropion SR in any of the measures of sexual functioning.

In the Clayton et al. study,[21] on the contrary, there was improvement in the frequency of sexual relationships. During four weeks, bupropion SR 150 mg was added two times a day to the antidepressant that the patients were taking. In the CSFQ, the patients of the bupropion group showed a significantly greater improvement in desire of initiating sexual activity and in the frequency of sexual activity compared with those who received the placebo. However, no differences were found in global sexual functioning, arousal, orgasm and interest in sexual thoughts and fantasies.

Better results were obtained in the clinical trials.

Labbate et al.[22] added 75 mg/day of bupropion to the treatment with SSRI in eight patients who had experienced a decrease in their sexual function since the initiation of the SSRI. After 4 weeks of treatment with bupropion, 50% of the participants scored their global sexual function as "much better" on a visual analogue scale. The four patients who responded satisfactorily were women.

Ashton and Rosen[23] investigated the efficacy of bupropion as antidote for SSRI-induced sexual dysfunction in 47 outpatients, with initial doses on demand and then up to 75 mg twice a day. Globally, 66% of the participants reported a reduction in the sexual dysfunction. Most occurred in all of the sexual response phases, with a tendency towards greater improvement in the desire and orgasmic

phases. Seven of the 47 patients (15%) abandoned combined treatment with bupropion due to side effects such as anxiety or tremor.

Another open study investigated the effects of combining bupropion SR with venlafaxine, paroxetine or fluoxetine in 19 patients with treatment-induced sexual dysfunction. After at least six weeks of monotherapy treatment with an SSRI/SRNI, 150 mg/day of bupropion were added for eight weeks. An improvement occurred in the three phases of sexual function (desire, arousal, and orgasm), but these differences were only statistically significant for orgasm in women and for global sexual functioning in the men. [24] Finally, Gitlin et al.[25] evaluated 24 patients (15 women and 9 men) with SSRI induced sexual side effects during a period of 7 weeks of combined treatment with bupropion, at a dose between 100 to 300 mg. Addition of bupropion provided an improvement in all the sexual side effects both in men (75% of response) and in women (46% of response). More than 50% of the improvement occurred within the first two weeks and at low doses (100-200 mg/day). Three subjects dropped out of the study due to intolerance of the stimulation side effects of bupropion.

BUPROPION PROFILE REGARDING BODY WEIGHT

Weight gain would be a foreseeable consequence of antidepressants with affinity for the histamine or 5-HT2C receptors. Bupropion, as it lacks relevant affinity for these receptors, does not cause weight gain. It is characteristic for mild weight loss to occur, equal to 1.5 kg with the initial treatment.[1]

Three randomized, double blind, placebo controlled studies evaluated body weight during eight weeks of treatment with bupropion in patients with major depression.

Settle et al. collected data from three similar studies that included 987 subjects treated with bupropion SR (100-400 mg/days) and 385 subjects treated with placebo. From the baseline to the end of the study, the patients treated with bupropion SR experienced dose-dependent weight loss. A daily dose of 100 mg was associated to a mean loss of 0.4 kg, 300 mg/day with a loss of 0.9 kg and 400 mg/day with a loss of 1.3 kg. No weight changes were observed in the placebo group.

A dose-dependent weight loss was also reported by Reimherr et al.[26] They evaluated changes in body weight in three treatment groups: placebo, bupropion SR, 150 mg/day (n = 121), bupropion SR 300 mg/day (n = 120). The placebo group experienced a weight loss of 0.2 kg, while the patients with bupropion 150 y 300 mg/day had a mean weight loss of 0.5 to 1 kg, respectively.

These results were confirmed in the third trial.[27] During eight weeks of treatment with bupropion at a dosage of 300-450 mg/day, the patients lost a mean of 1.1 kg compared to 0.2 kg in the placebo group.

A randomized, placebo controlled study investigated the long-term effects of bupropion SR on body weight of patients with major depression. During an 8-week open trial, the patients were treated with 300 mg of bupropion SR. The responders were randomly assigned to a double blind study with bupropion 300 mg (n = 210) or placebo (n = 213), for another 44 weeks. During the open phase, the patients lost a mean of 1.4 kg. This weight loss was maintained during the double blind study in the patients treated with bupropion while those treated with placebo returned to baseline weight. It should be stressed that the weight loss was greater in patients with a greater BMI at baseline.[28]

In the management of SSRI-induced overweightness, beginning with dietary advice and physical exercise, one therapeutic option may be that of switching to another antidepressant without risk of weight gain, such as bupropion.

The possible use of bupropion as an "antidote" (taken in combination) in case of SSRI-induced overweightness has not been established, since this possibility has not been evaluated in controlled studies.

DISCUSSION

This review studies the tolerability of bupropion and specifically its profile of side effects regarding sexuality and weight gain. The role that bupropion may play in the possibility of reversing these side effects when they are SSRI induced is also reviewed.

It is concluded that the profile of side effects is that expected according to its action mechanism, with a predominance of mouth dryness, nausea, insomnia, and agitation. These effects are only determinants to discontinue the drug in approximately 7% of patients. This means that in most of the cases, the side effects are mild or tolerable.

The review found very strong evidence that bupropion causes less sexual dysfunction than the SSRIs and very limited, but also important, evidence that bupropion added to the SSRIs may reverse some of the sexual side effects caused by the latter.

Finally, important evidence is found that bupropion, on the contrary to the SSRIs, does not cause weight gain but rather cause a mild weight loss in long-term treatment.

The possibility that bupropion may reverse the SSRI-induced weight gain has not been sufficiently evaluated. Therefore, this aspect needs to be evaluated in greater detail in the future.

Opinions of the experts of the work group

A work group was carried out in which the opinion on bupropion of the professionals with wide experience in its prescription was reviewed.

Specifically, they were asked to give their opinion on the tolerability of the drug and on its effects on sexuality and weight of the patients who were prescribed bupropion. Spontaneously, they also gave their opinion on other unauthorized indications (off-label) in which bupropion was useful for them.

The conclusions were the following:

Bupropion is a globally well-tolerated drug, although appearance of nausea, anxiety and insomnia in some patients has been reported. It was proposed that Bupropion would be better tolerated when used in combination than as monotherapy, although this assessment could be biased by the fact that if bupropion is added to a patient who is already taking an SSRI, we evaluate the tolerability of bupropion in a population that already tolerates SSRI, so that it is easier for them to also tolerate bupropion.

Regarding sexuality, there was general consensus that bupropion did not affect the sexual response as did the SSRIs. However, beyond the harmlessness of bupropion regarding the sexual function, different beneficial aspects of the drug in this area were suggested. In the first place, there is its capacity to restore sexuality affected by depression, when bupropion is used as a single antidepressant. In the second place, there is the possibility of using it in combination with and SSRI, as an "antidote" to combat SSRI-induced sexual dysfunction.

One of the persons attending suggested that efficacy of bupropion on sexual function was greater in women than in men. This statement, consistent with the results of some of the studies reviewed, would require specific studies in the future.

In regards to the role of bupropion and body weight, there is agreement by all of the professionals that bupropion did not cause weight gain and different opinions regarding whether its use entails weight loss. These opinions range between those considering that there was a clear weight loss and those who considered that there was no weight loss or that this was practically negligible. It was also suggested that by adding bupropion to a treatment with SSRI, the weight increase induced by it was "detained." As we have commented in the review and in the discussion, this assertation currently has limited scientific evidence.

In general, there is agreement that bupropion makes it possible to treat or counteract sexual dysfunction, weight gain and somnolence.

When going into more detail in the discussion on the tolerability and positive effects of the drug in these specific areas, the participants were of the opinion that the drug was also useful as a potentiator of other antidepressants and to treat pictures of fibromyalgia, chronic fatigue and attention deficit disorders.

IMPORTANT OR RELEVANT ASPECTS

We were able to draw the following conclusions from the bibliographic review and the discussion:

- Bupropion is an antidepressant drug with a low incidence of adverse effects.
- When these effects occur, they generally have mild to moderate intensity and do not require the withdrawal of the treatment, except in 7% of the patients.
- Bupropion has a very favorable profile regarding sexual function, which not only does not affect, but also potentiates and improves it, in both the depressed and non-depressed patients.
- Bupropion can reverse the SSRI-induced sexual dysfunction, so that it can be associated with these, making possible improvement of the sexual function and potentiating of the SSRI antidepressant effect.
- Bupropion also has a favorable profile regarding body weight, since taking it does not entail any weight gain and, if there is weight loss, it is of little importance.
- Although the SSRI-induced weight gain may be reversed by switching to bupropion, there is not sufficient evidence to advise the use of bupropion associated to the SSRI in an attempt to reverse the weight gain.

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