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A randomized, double-blind, placebo-controlled study of the efficacy and safety of bupropion for treating hypoactive sexual desire disorder in ovulating women

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OBJECTIVE

To compare the efficacy of sustained-release (SR) bupropion to placebo in treating hypoactive sexual desire disorder (HSDD) in ovulating women.

PATIENTS AND METHODS

After a 1-week, placebo lead-in phase, 232 treatment-seeking women with regular menstrual cycles were randomly assigned to bupropion SR 150 mg/daily (116) or placebo (116) for 12 weeks under double-blind conditions. Efficacy was assessed with the Brief Index of Sexual Functioning for Women (BISF-W), the Personal Distress Scale (PDS), the global efficacy question (GEQ; 'Did the treatment you received during the 12-week improve meaningful your sexual desire?') and overall patient satisfaction question ('Are you satisfied with the efficacy of your treatment?').

RESULTS

The mean (SD) composite score on the BISF-W, increased from 15.8 (2.6) and 15.5 (2.2) at baseline to 33.9 (4.2) and 16.9 (2.6) in the bupropion and placebo groups, respectively ($P = 0.001$). The odds ratio (95% confidence interval) for response in the bupropion group relative to placebo was 3.2 (2.1–6.3). The thoughts/desire score more than doubled in patients treated with bupropion ($P = 0.001$). At the 12-week evaluation the reduction in the PDS scale was 29.4% in bupropion and 4.7% in the placebo group ($P = 0.01$). In response to the GEQ, of patients in the bupropion and placebo groups, 65.3%, and 4.3%, respectively, responded 'Definitely yes' ($P = 0.001$). Of patients in the bupropion and placebo groups, 71.8%, and 3.7%, respectively, were definitely satisfied with the efficacy of their treatment, ($P = 0.001$). After 12 weeks of treatment, 82 women (78.1%) in the bupropion and five (4.9%) in the placebo group were willing to continue therapy ($P = 0.001$).

CONCLUSIONS

The results from this study indicate that bupropion SR is an effective and well-tolerated treatment for HSDD in ovulating women. Further controlled trials are warranted.

KEYWORDS

hypoactive sexual desire disorder, bupropion, treatment, ovulating women, libido

INTRODUCTION

Hypoactive sexual desire disorder (HSDD) is a common female sexual dysfunction (FSD) with reported rates of <10–30% [1–3]. In the fourth revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR), HSDD is defined as the persistent or recurrent deficiency or absence of sexual fantasies/thoughts, and/or desire for sexual activity that causes personal distress or interpersonal difficulties [4]. This definition is similar to that defined by The American Foundation of Urological Diseases (AFUD) definition of female sexual function disorders [5]: 'The persistent or recurring deficiency (or absence) of sexual fantasies/thoughts, and/or receptivity to sexual activity causing personal distress or interpersonal deficiencies'. Both definitions require that both low sexual desire and sexually related personal distress must be present for a diagnosis of HSDD.

Sexuality is a central factor to good health and sound relationships between women and their partners [6]. Satisfaction with a relationship strongly correlates with sexual satisfaction. Low sexual desire is associated with decreased levels of relationship satisfaction, and is highly distressing for many women and their partners [7]; ≈20% of these women seek medical help [2,8]. In the last decade there has been a resurgence of scientific interest in female sexual functioning. The main cause is a change in many societies' views on sexuality. Several pharmacological agents, some with central-acting mechanisms and some with androgenic effects, have been proposed in the treatment of different aspects of FSD such as arousal disorder and HSDD. In a double-blind placebo-controlled study, bremelanotide a centrally acting melanocortin receptor agonist, was effective and well tolerated in ovulating women with arousal disorder as a

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sole entity [9]. Despite clinical evidence of the effectiveness of testosterone in increasing sexual desire [10,11], the USA Food and Drug Administration (FDA) has not approved any androgen therapies for HSDD. However, testosterone transdermal patches have been approved by the European Agency for the Evaluation of Medicinal Products for use in HSDD. There is not yet an approved treatment for HSDD that is generally acceptable to women. An intact nigrostriatal dopaminergic pathway is essential for physiological copulatory behaviour [12]. An increase in sexual interest and/or libido is a well-known drug-induced complication of dopaminergic therapy in Parkinson's disease [13]. Caruso *et al.* [14] reported that daily apomorphine sublingual might improve the sexual life of women affected by sexual difficulties.

Bupropion [(+/–)-α-tbutylamino-3-chloropropiophenone] is a potent and selective dopamine-reuptake inhibitor with no clinically significant affinity for the serotonergic transporter or the serotonergic, cholinergic, adrenergic, or histaminergic receptors [15]. It also has subtle activity on noradrenaline reuptake. In a single-blind study by Segraves *et al.* [16] bupropion improved sexual functioning in 29% of 51 women (not depressed) with HSDD after several weeks of treatment. Iatrogenic HSDD is common in depressed patients who have been treated with selective serotonin re-uptake inhibitors (SSRIs). Bupropion sustained release (SR) is effective in treating all the major categories of SSRI-induced sexual side-effects [17]. In addition, prosexual effects of bupropion have been reported in several studies [5]. The beneficial effects of bupropion on HSDD in premenopausal women have also been reported [18]. Thus we conducted a double-blind placebo-controlled randomized study to address the effects of bupropion on HSDD in ovulating women.

PATIENTS AND METHODS

The study population comprised 268 women (aged 20–40 years) who were referred to one author (M.R.S.) from primary-care physicians, or sought treatment themselves, from February 2006 and March 2008. An initial diagnosis of HSDD was made during direct interviews conducted by a trained and experienced interviewer; all interviews were conducted by the same interviewer. The women were asked a series of direct questions with categorical responses pertaining to changes in their sex life, including decreases in the levels of desire and sexual activity that disturbed them; these questions were consistent with the definition of the HSDD by AFUD [19].

The women in the study had regular menstrual cycles (mean cycle length 27.5 days, SD 3.2) with ovulation. The study included a 4-week screening phase preceding the double-blind phase, in which the women completed the Brief Index of Sexual Functioning for Women (BISF-W), a validated 22-item, self-reported inventory of sexual desire, activity, arousal, orgasm and satisfaction [20]. Both the qualitative and quantitative domains of female sexual function can be assessed by BISF-W.

All patients gave written informed consent to be screened; before they were interviewed the Human Ethics Committee approved the study protocol, which was conducted in accordance with the Declaration of Helsinki. All of the patients had received and had failed one or more previous treatments for HSDD in the last 2 years, including oral methyltestosterone (166, 61.9%), sublingual preparations (82, 30.6%), testosterone patches (88, 32.8%), and various topical and vaginal gels and creams (172, 64.2%); 202 (75.4%) had had more than one treatment.

During the screening period (week –6) all patients underwent a physical examination, including weight, height, heart rate, blood pressure and an echocardiogram. The following variables were also assessed: detailed medical, sexual and psychosocial history; current and past medical therapies; and sociodemographic variables including cigarette smoking and alcohol consumption. Blood samples were obtained on cycle days 12–17 from all patients to measure serum chemistry, haematology and hormonal profile, including: free, total and bioavailable testosterone; sex hormone-binding globulin; free and total oestradiol, and oestrone; FSH, LH and prolactin. The ovulatory cycle was confirmed using ultrasonography on days 10, 12 and 15 of the cycle, and serum progesterone concentrations were determined at days 21 and 25 of the cycle. The ovulation was documented when the serum progesterone level was >20 IU/mL.

Major depressive disorder was excluded according to DSM-IV criteria [21]. To be able to exclude other major psychological disorders, all patients completed the Dissociative Experiences Scale [22], the Hamilton Rating Scale for Anxiety [23], and the Liebowitz Social Anxiety Scale [24].

The inclusion/exclusion criteria are summarized in the Appendix. Patients visited the research centre twice during the 4-week screening period to evaluate their eligibility to participate in the study. Only patients with HSDD, normal serum biochemistry, haematology and hormonal profile, and normal psychological assessments, were included. Patients had to have had normal menstrual cycles with ovulation, and had to be in a stable satisfying relationship with a sexually functional partner for at least 1 year before the study. Women with a history of diabetes mellitus, impaired hepatic or renal function, neoplasia, psychiatric disorder, taking any nutritional supplementation or medication with a known influence on sexual function during the previous 6 months, such as androgens, antiandrogens, SSRIs, tricyclic antidepressants, progestins, and α-blockers; a history of physical limitation; smoking, alcohol and/or drug abuse; or taking hormone therapy or oral contraceptives, were excluded from the study. Exclusion criteria also included current pregnancy or lactation; history of sexual trauma, relationship disturbances, cerebrovascular disease, or other serious medical conditions. For determining relationship problems, patients and their husbands were interviewed alone in private, without their partners. Diagnostic criteria for partner relational problems were: 'pervasive sense of unhappiness with the relationship, thoughts of divorce/separation, perceived need for professional help for the relationship, and significant impact of the relational dissatisfaction on behavioural, cognitive, or affective systems' [25]. Of 268 screened patients, 232 met the inclusion and exclusion criteria and consented to proceed with the study protocol.

Before randomizing patients into different groups, all the patients were entered into the placebo lead-in phase (week –2). All patients received single-blind placebo for 2 weeks. Those who showed an increase of ≥20% in the 'thoughts/desire' domain of BISF-W (placebo responders) were excluded. Eligible women were then randomly assigned in a 1 : 1 ratio by the method of random permuted blocks to receive 150 mg/day of bupropion SR (group 1, 116) or matching placebo (group 2,

116) for 12 weeks. Concomitant medications known to affect the results were prohibited during the study period. The randomization procedure was performed by another person who was geographically and operationally independent of the study investigators. Both the study personnel and the patients were unaware of the treatment assigned.

Baseline measurements were obtained on day −1; thereafter, patients visited the study centre biweekly during the 12-week study period to evaluate their general condition, treatment results and treatment-emergent adverse events (TEAEs). At each visit, the patients were asked about any medical symptoms and/or possible side-effects and were given the BISF-W and the Personal Distress Scale (PDS). The global efficacy question (GEQ; 'Did the treatment you received during the 12-week improve meaningful your sexual desire?') and overall patient satisfaction question ('Are you satisfied with the efficacy of your treatment?') were also assessed to evaluate the efficacy of bupropion. Women were also asked about their willingness to consider continuing treatment after the end of the study.

The BISF-W was originally developed in 1994 by Taylor *et al.* [20], then modified to prevent overlap of domains and a scoring algorithm was developed [26]. The BISF-W can discriminate between depressed, sexually dysfunctional, and healthy patients, and has enough sensitivity to detect treatment-induced changes in the overall total score of the BISF-W. The BISF-W assesses seven domains of sexual functioning in women, including: thoughts/desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction, and problems affecting sexual function. The range of composite scores is from −16 (poor function) to +75 (maximum function). The mean values in normal women with partners are as follows: composite score, 33.6; thoughts/desire, 5.3; arousal, 6.2; frequency of sexual activity, 3.9; receptivity/initiation, 8.9; pleasure/orgasm, 4.9; relationship satisfaction, 8.9; and problems affecting sexual function, 4.5. Adding the scores of the domains one to six and subtracting the seventh domain gives the individual composite score.

The PDS is a seven-item, self-administered questionnaire designed to measure distress due to lack of sexual desire [27]. Each item of the PDS has six scoring options, including always (1), very often (2), often (3), sometimes (4), seldom (5), or never (6). The PDS score was computed by the summing the scores for the items on the scale. The raw score was transformed to a 0–100 scale using the following formula [28]: [(actual raw score − lowest raw domain score possible)/(highest raw domain score possible − lowest raw domain score possible)] × 100. Scores of 0, 20, 40, 60, 80 and 100 on the PDS correspond, on average, to the following categories of response: 'never', 'seldom', 'sometimes', 'often', 'very often', and 'always' distressed about a lack of interest in sex, respectively. A low domain scores represented low patient distress [28].

Safety assessments included a medical history and physical examination, weight, electrocardiogram, routine laboratory studies, and spontaneous report of AEs during the study period at each follow-up visit. TEAE terms were coded to preferred terms, as specified in the Medical Dictionary for Regulatory Activities, version 7.

Values are given as the mean (SD) unless otherwise stated. Intent-to-treat analyses were used for all efficacy variables and included all patients who had undergone the baseline evaluation and had at least one valid efficacy assessment after baseline. The principle of last observation carried forward was used for patients who did not complete the full study schedule. The sample size of 102 patients per treatment group was chosen to obtain an overall 80% power to detect differences in changes from baseline in BISF-W composite score at the 0.05 level of significance. Considering possible withdrawal rates, 14 additional patients (10%) were included to ensure sufficient power, resulting in 116 patients per arm and 232 in total. The Wilcoxon signed-rank test was used to evaluate measures between baseline and after each treatment. The Mann–Whitney U-test was used to compare quantitative variables. Categorical variables were compared with using the chi-square test with Yates correction, or Fisher's exact test, when necessary. Scores for all domains were compared before and after treatment using a two-tailed Student's *t*-test. Derived BISF-W binary variables (improvement or no improvement) were analysed by logistic regression to determine the odds ratio (OR) and 95% CI for bupropion compared with placebo. CIs were calculated using the exact binomial method. The incidence of AEs was compared using the chi-square and independent samples *t*-tests.

RESULTS

The baseline characteristics of the patients are given in Table 1; none of the differences in demographic and clinical characteristics between groups was statistically significant. Of the 232 women randomized in the study, 223 (96.1%) completed at least one efficacy assessment after treatment and were analysed (Fig. 1). Twenty-four women (10.3%) did not complete the study after randomization; eight for lack of efficacy (two in the bupropion, five in the placebo group), three withdrew consent (one bupropion, two placebo), five because of AEs (three bupropion, two placebo) and eight lost to follow-up (four in each group). Compliance was similar in both treatment groups.

The mean (SD) composite score on the BISF-W, increased from 15.8 (2.6) and 15.5 (2.2) at baseline to 33.9 (4.2) and 16.9 (2.6) in the bupropion and placebo groups, respectively ($P = 0.001$) (Table 2). The OR (95% CI) for the response in the bupropion group relative to placebo was 3.2 (2.1–6.3). The thoughts/desire score more than doubled in patients treated with bupropion ($P = 0.001$). There was a statistically significant increase in the seven domains of BISF-W in the bupropion group vs placebo in the 4-week period beginning at 2 weeks. These beneficial effects continued to increase until 8 weeks. The major effect of bupropion on the BISF-W domains was achieved by 8 weeks, with a modest further improvement by 12 weeks (Fig. 2). The increases in all seven of the BISF-W domains of sexual functioning were significantly greater than those with placebo ($P = 0.01$ for both receptivity/initiation and relationship satisfaction domains, and $P = 0.001$ for the five remaining domains). The scores for frequency of sexual activity, thoughts/desire and pleasure/orgasm showed the greatest increase from baseline at the end of trial (117.6%, 104.8% and 83.3%, respectively; Fig. 3). The decrease in PDS scores in the bupropion group at 4 weeks was significantly greater than the decrease in the placebo group. At the 12-week evaluation the reduction in the PDS score was 29.4% in the bupropion and 4.7% in the placebo group ($P = 0.01$; Table 2).

Mean (SD) or *n* (%) characteristic	Bupropion (116)	Placebo (116)
Age, years	29.7 (5.2)	29.2 (5.3)
Patient	29.7 (5.2)	29.2 (5.3)
Partner	34.7 (4.1)	34.2 (4.3)
Duration (years) of:		
marriage	7.4 (2.1)	7.4 (2.1)
HSDD	4.2 (1.8)	4.4 (1.7)
Education level		
Patients		
High School	44 (37.9)	46 (39.7)
Graduate	72 (62.1)	70 (60.3)
Husbands		
High School	51 (44)	52 (44.8)
Graduate	65 (56)	64 (55.2)
Occupational status		
Unemployed (and/or housewife)	36 (31)	35 (30.2)
Employed	80 (69)	81 (69.8)
Pregnancy and delivery		
Present	86 (74.1)	83 (71.6)
Absent	30 (25.9)	33 (28.4)
Body mass index, kg/m^2		
>30	21 (18.1)	22 (19)
<25	74 (63.8)	76 (65.5)
Mean no. of children	1.8 (0.4)	1.8 (0.2)

TABLE 1
The baseline characteristics of the patients; none of the differences were significant

FIG. 2. Changes in the composite BISF-W score.

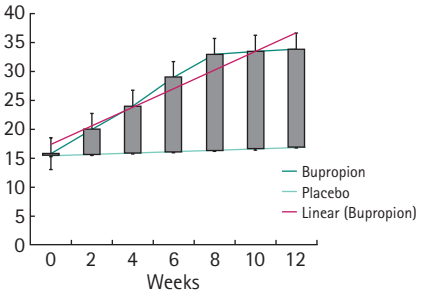


*FIG. 3. Changes from baseline on the BISF-W domain scores. **A**, composite; **B**, thoughts/desire; **C**, arousal; **D**, frequency of sexual activity; **E**, receptivity/initiation; **F**, pleasure/orgasm; **G**, relationship satisfaction; **H**, problems affecting sexual function.*

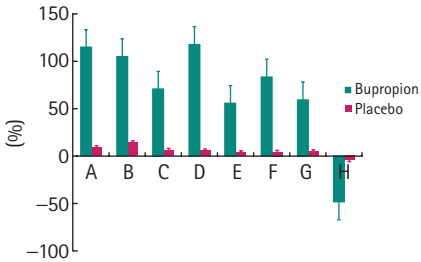


FIG. 1. A flow chart of recruited patients.

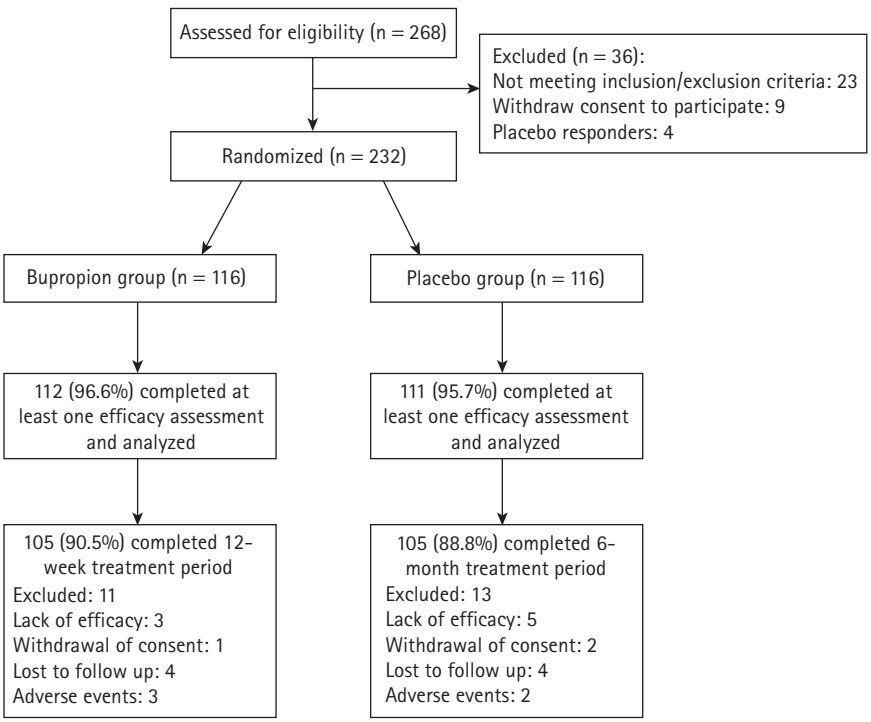
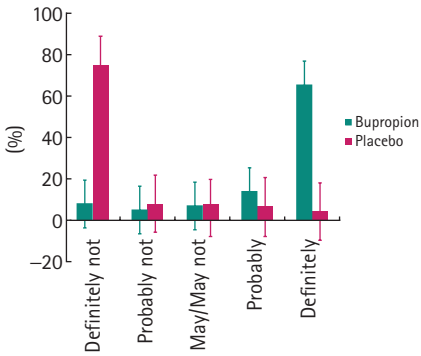


FIG. 4. Responses to the GEQ; 'Did the treatment you received during the 12 weeks improve meaningfully your sexual desire?'

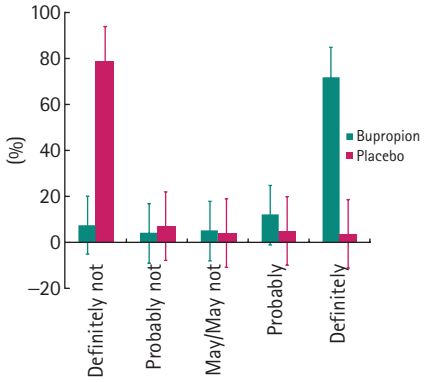


In response to the GEQ; 'Did the treatment you received during the 12-week improve meaningful your sexual desire?' of patients in bupropion and placebo groups, 65.3%, and 4.3%, responded 'Definitely yes', respectively (P = 0.001) (Fig. 4). Women who reported a definitely meaningful improvement in sexual desire had a statistically significantly greater

TABLE 2 Mean (SD) scores on the BISF-W and PDS with treatment and after 12 weeks of treatment

	Baseline			12-weeks				
Domains	Bupropion	Placebo	*P*	Bupropion	% change	Placebo	% change	*P*
No. of patients	112	111		112		111		
Composite score	15.8 (2.6)	15.5 (2.2)	NS	33.9 (4.2)	+114.6	16.9 (2.6)	+9	0.001
Thoughts/desire	2.1 (0.17)	2.1 (0.16)	NS	4.3 (0.22)	+104.8	2.4 (0.18)	+14.3	0.001
Arousal	3.4 (1.12)	3.2 (1.18)	NS	5.8 (1.24)	+70.6	3.4 (0.12)	+6.3	0.001
Frequency of sexual activity	1.7 (0.12)	1.8 (0.10)	NS	3.7 (0.42)	+117.6	1.9 (0.14)	+5.6	0.001
Receptivity/initiation	5.4 (1.18)	5.3 (1.17)	NS	8.4 (2.16)	+55.6	5.5 (1.12)	+3.7	0.01
Pleasure/orgasm	2.4 (0.28)	2.3 (0.27)	NS	4.4 (1.66)	+83.3	2.4 (0.21)	+4.3	0.001
Relationship satisfaction	6.4 (1.46)	6.2 (1.41)	NS	10.2 (2.86)	+59.4	6.5 (1.13)	+4.8	0.01
Problems affecting sexual function	5.6 (1.54)	5.4 (1.42)	NS	2.9 (0.26)	−48.2	5.2 (1.17)	−3.7	0.001
PDS score	62.4 (21.14)	64.1 (22.12)	NS	44.2 (16.18)	−29.4	61.1 (21.14)	−4.7	0.01

FIG. 5. Responses to the overall patient satisfaction question 'Are you satisfied with the efficacy of your treatment?'



AE	Bupropion (112)	Placebo (111)	*P*
Headache	10 (8.9)	7 (6.3)	0.06
Insomnia	8 (7.1)	6 (5.4)	0.06
Dry mouth	8 (7.1)	4 (3.6)	0.03
Nausea	7 (6.3)	3 (2.7)	0.01
Muscle aches	7 (6.3)	2 (1.8)	0.01
Loss of appetite	5 (4.5)	1 (0.9)	0.01
Constipation	5 (4.5)	2 (1.8)	0.01
Stomach ache	5 (4.5)	2 (1.8)	0.01
Fatigue	4 (3.6)	4 (5)	
Tinnitus	4 (3.6)	1 (0.9)	0.01
Diarrhoea	3 (2.7)	0	0.02
Somnolence	2 (1.8)	4 (3.6)	0.02

TABLE 3 Summary of AEs over the 12-week period in the intent-to-treat population

increase from baseline in the BISF-W composite score (OR 4.8, 95% CI 2.6–7.2, $P = 0.001$). Among the women who definitely did not benefit from bupropion treatment, the mean changes from baseline on all seven domains of BISF-W were small and insignificant.

Patients were also asked about overall satisfaction rate; of those in the bupropion and placebo groups, 71.8% and 3.7% were definitely satisfied with the efficacy of their treatment, respectively ($P = 0.001$; Fig. 5). By 12 weeks, 81% and 34% of sexual episodes were satisfying in the bupropion and placebo groups, respectively ($P = 0.001$). Women who benefited from bupropion treatment were also significantly more likely to indicate willingness to continue treatment. After 12 weeks of treatment, 82 women (78.1%) in the bupropion and five (4.9%) in the placebo group were willing to continue therapy ($P = 0.001$).

Table 3 shows the most common AEs reported by patients in the two groups; there was no serious AE. In all, 32 (28.6%) and 26 (23.4%) patients reported AEs in the bupropion and placebo groups, respectively ($P = 0.03$). The most common AEs with bupropion included headache (8.9%), insomnia (7.1%), dry mouth (7.1%), nausea (6.3%), and muscle aches (6.3%). Of the three patients in the bupropion group who prematurely withdrew from the study due to AEs, one reported headache, another reported somnolence and nausea and a third reported insomnia.

DISCUSSION

This is the first study of the use of oral bupropion in ovulating women with HSDD. We studied ovulating women whose reproductive hormones had normal levels. The study showed that bupropion SR 150 mg/day significantly improved the BISF-W composite score and significantly decreased the PDS score. During the 12-week study, bupropion SR was associated with a 114% increase in the BISF-W composite score. A significant difference between active drug and placebo was already apparent after 2 weeks of treatment (Fig. 2). In this study, 75% of patients had received one or more previous treatments for HSDD, with limited success. Lack of desire for sex is a prevalent problem in ovulating women. In a European study, the percentage of women across four Western European countries (France, Germany, Italy and the UK) classified with low sexual desire ranged from 16% of regularly ovulating women to 29% of surgically menopausal women of the same age group (aged 20–49 years) [29]. In the American survey conducted by Laumann *et al.* [8] a lack of sexual desire was reported by 32% of women. For many years androgens have been used as a treatment for decreased sexual desire. Beneficial effects of various testosterone

products on HSDD have been shown in phase III studies [10] and testosterone transdermal patches have also been approved by the European Agency for the Evaluation of Medicinal Products for treating HSDD. However, in December 2004, the USA FDA declined to approve a testosterone-delivery patch, Intrinsa® (Proctor & Gamble Pharmaceuticals, Cincinnati, OH, USA), which had significant efficacy in postmenopausal women, due to concerns over potential long-term safety [11]. In a recent literature review by Schover [11], she concluded that testosterone supplementation should not be prescribed to women with low sexual desire unless long-term studies can confirm its efficacy and safety. However, low serum androgens in pre- and postmenopausal women with decreased sexual desire have been documented in other studies [30,31]. In one study, Guay [30] measured total and free testosterone levels in 12 premenopausal women complaining of diminished libido. Of the 12 women, eight had low or immeasurable levels of testosterone despite having regular menstrual cycles. Treatment with oral dehydroepiandrosterone 50–100 mg/day restored sexual desire in six of the eight women.

The concept of low sexual desire as a state of virtue has started to change during the past decade. At present hypoactive sexual desire is highly worrying for many women and must be well managed. Little is known about the aetiopathology of HSDD. Understanding the exact pathophysiology of disease is critical to diagnosis and effective treatment. The effectiveness of bupropion for treating HSDD with unknown aetiology has been evaluated by some researchers. In a blinded study, Segraves *et al.* [18] showed that premenopausal women treated with an escalating dose of bupropion SR were more likely to report a meaningful benefit than women receiving placebo. Our findings are consistent with previous studies that have shown the beneficial effects of bupropion on different aspects of sexual functioning in women [16,32]. In addition, some studies showed that bupropion can effectively manage SSRI-induced sexual dysfunction [17,33]. Bupropion is an indirect dopamine and noradrenaline agonist, but has no significant effect on serotonin [34]. A correlation between increased activity in both dopaminergic and noradrenergic systems with increased sexual responsiveness was reported previously [35]. In 1954, Olds and Milner [36] identified the 'pleasure centre' and later neuropharmacological research identified dopamine as key in this 'pleasure centre'. Bupropion also has a pro-sexual effect in humans. A proposed mechanistic hypothesis for this pro-sexual effect is enhancing dopaminergic and noradrenergic transmission [34]. Assessing sexual desire is very difficult. A woman, not sexually motivated at the time, might engage in sexual activity with her partner for several reasons unrelated to sexual drive [37]. Therefore, appropriate patient selection is an important issue in conducting clinical trials for HSDD.

There are legitimate concerns about AEs; most were mild to moderate, and on the basis of our findings, treatment with bupropion SR 150 mg/day was not associated with serious AEs. Currently, there are several measures to assess FSD and sexually related personal distress in women, such as the Female Sexual Function Index, BISF-W, Female Sexual Distress Scale and the PDS; all are valuable tools. In the present study we used the BISF-W and PDS questionnaires; we believe that the BISF-W dimensions of 'relationship satisfaction' and 'frequency' do not have obvious corresponding dimensions in the other instruments. In addition, in the phase III clinical trials, the PDS was able to measure treatment effects that were clinically meaningful to the women [10].

The placebo response rate (≈5%) in this study was low, probably because these women had tried and failed to respond to at least one drug therapy previously. In addition, before randomization of patients, all were entered into the placebo lead-in phase and placebo responders were excluded. Interestingly, the AEs reported here were lower than those reported previously, e.g. in this study, of patients in bupropion group, 9% reported headache, while the reported rate of headache with bupropion in some studies is as high as 35% [38,39]. We could not fully explain this issue. However, most common AEs associated with bupropion (headache, insomnia, nausea and dry mouth) are subjective symptoms. Reporting a symptom depends on how distressing patients found a symptom. In addition, the type of disease for which patients are being treated might influence the reported rate of AEs. Most studies with bupropion have been conducted in patients with psychiatric disorders such as depression and alcoholism. In the present study, these AEs were tolerated, and three of the patients discontinued the medication due to AEs.

The current study has some advantages. First, it was placebo-controlled; patients were unaware of the treatment allocated. Second, the study group comprised middle-class women who were seeking medical help for their problem. Last, there were sufficient women assessed for valid statistical calculations. A limitation of the study was the source of the women; the population comprised a consecutive series of women who sought treatment for sexual dysfunction. These patients had already failed at least one other medical treatment for HSDD, and therefore the results must be interpreted cautiously as they might not apply to the general population with HSDD. Our results suggest that bupropion should be the subject of larger studies in a more representative population sample.

In conclusion, the results of this controlled clinical trial show that bupropion SR significantly improved HSDD in ovulating women, as measured by several endpoints. Bupropion was relatively well tolerated with predictable adverse effects. Further studies are warranted to better elucidate the role of dopaminergic system in female sexual functioning and to replicate our results.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HSDD**, hypoactive sexual desire disorder; **FSD**, female sexual dysfunction; **PDS**, Personal Distress Scale; **BISF-W**, Brief Index of Sexual Functioning for women; **GEQ**, Global Efficacy Question; **SR**, sustained release; **FDA**, Food and Drug Administration; **DSM**, Diagnostic and Statistical Manual of Mental Disorders; **AFUD**, American Foundation of Urological Diseases; **SSRI**, selective serotonin re-uptake inhibitor; **(TE)AE**, (treatment-emergent) adverse event; **OR**, odds ratio.

APPENDIX

Inclusion criteria

1 Diagnosis of HSDD, with normal serum biochemistry, haematology, and hormonal profile.
2 Women with regular menstrual cycles (mean cycle length 27.5 ± 3.2 days) with ovulation.
3 Women with normal psychological assessments.
4 Women in a stable satisfying relationship with a sexually functional husband for at least 1 year.
5 Not pregnant and not lactating.

Exclusion criteria

1 Women with a known anatomical or physiological diagnosis that would interfere with normal sexual function.
2 Diabetes mellitus, impaired hepatic or renal function, neoplasia, cerebrovascular disease, psychiatric disorder, or other serious medical conditions.
3 History of physical limitation; smoking, alcohol and/or drug abuse.
4 Taking hormone therapy or oral contraceptives.
5 Taking any nutritional supplementation or medication with a known influence on sexual function during the previous 6 months.
6 Current pregnancy or lactation.
7 History of sexual trauma or relationship problems with partner, which in the opinion of the investigator (M.R.S.) would preclude effective treatment.