Review

Bupropion: Efficacy and safety in the treatment of depression

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INTRODUCTION

It is considered that depressive disorders, whatever their clinical forms, are among the most frequent psychiatric conditions. In a study performed in 2004, Waraich et al. indicated that the annual prevalence of major depressive disorder (MDD) was 4.1% and they estimated that 6.7% of the population would have one or more depressive episodes at some point during their life time.[1] This prevalence coincides with the data from the *European Study of the Epidemiology of Mental Disorders (ESEMeD) Project* (2004) carried out in 21,425 persons in six European countries. That study estimated an annual prevalence of depressive disorders in adults of 4% and prevalence of depression close to 13% during one's life.[2] However, other studies have found much higher MDD prevalence values that approach 20% in men and 30% in women during the life span.[3]

If we refer to studies carried out in our country, the first results from the analysis of the ESEMeD study in Spain, with a sample of 5473 persons and conducted within the frame of the European survey between 2001 in 2002, revealed that the most prevalent mental disorder in the population is major depressive episode.[4] A prevalence-life (at any time during their life) of 10.5% and a prevalence-year (in the last year) of 3.9% were observed.[5]

According to the Statistical Yearbook of the National Health Survey of Spain (National Institute of Statistics) published in 2007, and with the data corresponding to the year 2003, 4.56% of the population suffers chronic depressive disorder, this being the seventh diagnosis in frequency, only behind that of cardiovascular and respiratory apparatus-related diseases.[6] Prevalence-year of depression increases with age: between 1.14% in those under 34 years of age and 10.34% in persons between 65 and 74 years of age. It is elevated in the 55 to 64 year age group (9.35%), although it slightly decreases (9.23%) in the group over 75 years of age. This is a fact to keep in mind in developed countries (Table 1).[6]

The DSM-IV-TR establishes symptoms such as the depressive mood state, sadness, sensation of emptiness or irritability, body weight changes (loss or gain), modification of appetite, insomnia or hypersomnia, agitation or psychomotor slow down, feelings of uselessness or guilt and decreased concentration capacity, among other, as diagnostic criteria of the MDD.[7]

The International Classification of Disease (ICD), in its 10th version (ICD-10), defines MDD as the maintained presence of a decreased mood state, reduced energy and marked tiredness after small efforts, frequently associated to sleep and appetite disorders, reduction in capacity to experience pleasure and interest and concentration difficulty. The episode may be considered according to its severity (mild, moderate or severe), with or without psychotic symptoms, based on the number and types of symptoms presented in an individual, or by its intensity and frequency. The MDD may be manifested by a single episode or recurrent episodes.[8]

To diagnose MDD, there should be a sufficient number of the different symptoms (DSM-IV-TR contemplates a minimum of 5 out of the 9 symptoms described) for at least 2 weeks. However, shorter periods are accepted in cases of unusually rapid or severe onset. [7]

From the pathophysiological point of view, affective disorders are a biologically heterogeneous disease in which, among others, alterations have been described in the neurotransmission systems related with serotonin (5-HT), norepinephrine (NE) and dopamine (DA). The monoaminergic hypothesis of depression arose shortly after the appearance of the first antidepressants, tricyclics and monoamine oxidase inhibitors (MAOI), when it was observed that the action of these drugs was mediated at least partially by their effect on catecholamines (NE and DA) or indolamines. Serotonin has played a very outstanding role in the neurobiological hypotheses of

Table 1 **Chronic disease and diagnosis of the disease. Year 2003. Percentage of population by age**

	Total	0 - 34 years	35 - 44 years	45 - 54 years	55 - 64 years	65 - 74 years	≥75 years
Depression	4.56	1.14	4.19	6.22	9.35	10.38	9.23
Other mental illnesses	1.71	1.26	1.73	1.29	1.58	1.57	5.64

Source: Anuario Estadístico (Page 234) from the Encuesta Nacional de Salud (INE)

depression. This has motivated the preponderance of the SSRIs for many years in its treatment (or, to the contrary, the SSRIs have favored the preponderance of serotonin), and after, the NE with the resulting introduction of the SNRIs. On its part, the DA was somewhat pushed into the background, in spite of the important relationship between DA and depressive disorders and the demonstrated efficacy of dopaminergic drugs in these disorders and, that in the entire history of the psychopharmacology, only one drug with DA action, that is normfensine, withdrawn from the market due to its hematic effects, has stood out until the appearance of Bupropion (BUP).[9]

BUP is a drug that exerts its effect through NE and DA reuptake inhibition.[10] This drug is the only one currently available that is capable of selectively inhibiting these two catecholamines, without having significant effects on the reuptake of 5-HT and absence of monoamine oxidase (MAO) inhibition. Its chemical structure is not related with that of the tricyclic, tetracyclic antidepressants or with the 5-HT reuptake inhibitions.[10] Its availability in the USA goes back to 1989, with an extensive history of uses in patients diagnosed of MDD. Bupropion hydrochloride (HCl-BUP) was initially approved in its immediate release (IR) formulation, with usual doses of 300 mg/day (100 mg/dose, three doses per day). In 1996, the sustained release (SR) presentation form was sold on the basis of its bioequivalence with the IR formulation and its two times a day administration form. More recently (2003 in the USA and 2007 in Europe), its modified release ("*extended release*," XL/XR) presentation form and single daily administration is being sold. The maximum approved dose in the USA is 400 mg for the SR formulation and 450 mg/day for the IR and XL formulations.[11] Maximum approved dose in Spain for the XR formulation is 300 mg/day.

Prior to its initial approval, BUP demonstrated its clinical efficacy, tolerability and safety versus placebo and other antidepressants such as amitriptyline,[12-16] doxepine[17] and imipramine as active control.[18]

This paper aims to update the data published on the efficacy and effectiveness of BUP in the treatment of MDD. On the other hand, in this paper, we include a specific section on expert's opinion, in which the authors present the data within a clinical context in order to collaborate with the physicians who commonly manage this condition to better understand what role BUP may play in the treatment of these patients.

CHEMICAL AND PHARMACOLOGICAL CHARACTERISTICS

Chemical structure

Chemically, BUP is a **monocyclic phenylbutylamine** of the **aminoketone group**, which could be associated with an effect profile different from that of other antidepressant drugs. [19] It is also known as amfebutamone.

Neuropharmacology

On the contrary to other antidepressants, its primary action mechanism is neuronal reuptake inhibition of NE and DA[20] without significant serotonergic effects. On the other hand, the first studies already showed that BUP lacked anticholinergic and direct sympathomimetic activity and its cardiac depressant activity was at least 10 times lower than that shown by tricyclic antidepressants. The discovery of BUP therefore meant having a drug with a new action mechanism and a favorable profile of side effects, which offered better safety and tolerability regarding other current antidepressant treatments.[21]

The first data obtained *in vitro* showed the characteristics of BUP as a dual DA and NE reuptake inhibitor[11] without specific affinity for postsynaptic histamine, muscarinic, alpha or beta adrenergic or serotoninergic receptors and without MAO inhibitor action.[22] Bredeloux compared the BUP actions with those of dexamphetamine in regards to its effect on DA reuptake and release, concluding that the effect of BUP and its metabolites, both *in vivo* and *in vitro*, are similar on DA reuptake inhibition but that BUP does not affect release while

dexamphetamine does affect it.[23] Even when the primary effect of BUP seems to be related with DA reuptake inhibition, functional neuroimaging studies with SPECT and the percentage of BUP binding to the DA transporter indicates that some other action mechanism could be involved in its antidepressant effect.[24]

In fact, preclinical and clinical data are those that indicate that the antidepressant action mechanism of BUP would depend on the reuptake inhibitor effect of both DA[25] and NE.[10, 26] However, the inhibitor effect on DA reuptake is greater than on any other of the biogene amines, probably by an action directly on the DA transporter,[27, 28] although it is also a weak inhibitor of NE reuptake.[22] On the other hand, BUP does not have an amphetamine type stimulating activity since it does not increase DA release, as we have previously mentioned.[29] Indeed, relatively recent studies[30] suggests that BUP acts as a noncompetitive antagonist of some nicotinic receptors.

Because it lacks actions on some serotonergic mechanisms, it has a lower risk of side effects on the sexual sphere than that of other antidepressants.[31]

Depressive mood state is considered to be one of the core symptoms of MDD. Several functional neuroimaging studies have shown an association between depressive mood, sadness and abnormal neuronal activity in the prefrontal, anterior cingulate and orbitofrontal cortices. Depressed mood would be associated with low levels of 5-HT, NE and DA, while antidepressants that elevate the levels of depressive disorders in these neurotransmitters have been shown to produce improvement of this symptom.[32, 33]

It has been suggested that the reduction in motivation, in capacity to experience pleasure (anhedonia), of response to reward and loss of interest are associated with a decrease in dopaminergic activity.[34-36] It has also been observed that DA levels in plasma negatively correlate with the score on the Hamilton Rating Scale for Depression (HAM-D) in MDD[37] and, parallelly, low levels of DA and its metabolites in serum, cerebrospinal fluid and urine of persons who commit suicide have been uniformly found.[9]

Dysfunction of the mesocortical-limbic dopaminergic system, that innervates limbic structures such as the nucleus accumbens, amygdala and ventral hippocampus and of cortical structures such as prefrontal cortex, may provoke a decrease in motivation, interest and incapacity to experience pleasure similar to the symptoms observed in MDD. Thus, antidepressants that increase DA release in the mesocortical-limbic regions seem to specifically improve anhedonia, lack of motivation and energy.[32, 38] Very recent studies conducted in rats treated with adrenocorticotropic hormone (ACTH) and using the forced swim test suggest that the antidepressant effect of BUP could depend on the DA levels in the *n. accumbens*.[39]

It is not exactly known what the pathophysiology of the symptoms of fatigue and loss of energy in MDD is. Hypothetically, the areas of the brain known as striate and/or cerebellum that control the motor functions may be involved in physical fatigue. The cortical areas (dorsolateral prefrontal cortex) may be related, on their part, with psychic fatigue. If this is true, antidepressants increasing noradrenergic, dopaminergic activity or both may be beneficial for depressed patients with predominant symptoms of fatigue and loss of energy.[40-42]

On another part, hyperactivity of the amygdala has been related with an increase in prevalence of anxiety and negative affects symptoms: irritability, aggression, self-disdain, guilt and suicidal thoughts.[43] Antidepressants that increase serotonergic and/or noradrenergic activity have been shown to be effective in the treatment of patients with depression and associated anxious symptoms[44] (Figure 1).

Finally, in a recent review,[45] the importance of the DA and NE systems is stressed for the control of different prosencephalic functions whose alterations contribute to psychiatric conditions such as depression. Given the interconnectivity of the monoaminergic neuronal networks, any action on a system would have a repercussion on another and the analysis of these networks and their dysfunctions suggests that drugs with selective or dual

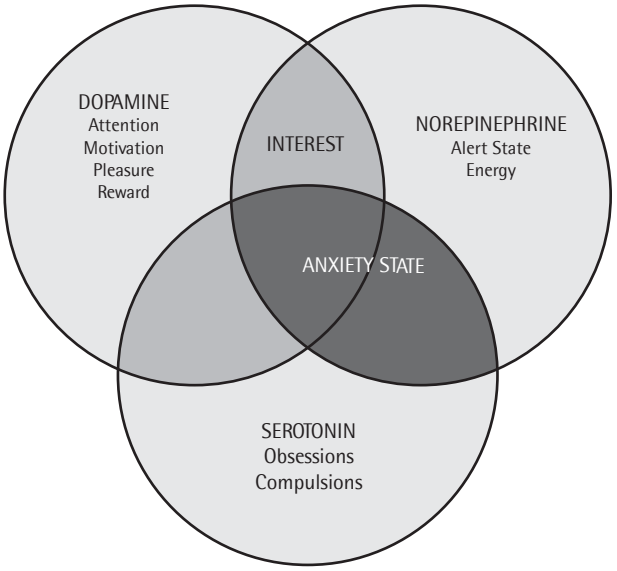

Figure 1 Neurotransmitters and their participation in the mood state[142-147]

action on DA or NE as BUP will have potent therapeutic effects.

Pharmacokinetics

BUP is always administered orally. After its administration, BUP is rapidly and almost 100% absorbed by the intestine, probably due to its low molecular weight and liposolubility. Its half life, in the modified release formulation (XR), is 21 hours. The drug is metabolized in the liver and it is excreted through the kidney. The stable plasma concentration of the drug and its active metabolites is reached at 5 to 7 days after initiation of its administration. The hepatic cytochrome P450 (CYP) 2B6 catalyzes the hydroxylation of the side chain (terbutilene group) of BUP to form an active metabolite, hydroxybupropion. Two less active metabolites, threohydrobupropion and erythrohydrobupropion, are formed by reduction of the ketonic side chain.[46] The isoenzymes CY1A2, 2A6, 2C9, 2D6, 2E1 and 3A4 also play a role in the metabolism of the original drug, but in a smaller proportion.[31, 47]

BUP is metabolized extensively in the human being, and its active metabolites reach higher concentrations than the BUP per se. The most significant active metabolite is hydroxybupropion, which is believed to be responsible for most of its clinical effects. Finally, the active metabolites are subsequently metabolized into inactive metabolites.[48, 49]

The maximum plasma concentrations of BUP XL/XR are obtained at five hours, at seven hours for hydroxybupropion and at eight hours for threohydrobupropion and erythrohydrobupropion.[50] The plasma levels of erythrohydrobupropion are similar to those of BUP, while the area under the curve (AUC) of threohydrobupropion is approximately five times greater, and that of hydroxybupropion three to 10 times greater than that of BUP. Its absolute bioavailability is unknown. However, the urinary excretion indicates that at least 87% of the BUP dose is absorbed.[11] Its absorption and bioavailability are not directly related with food intake.[11] No relationship has been found between gender and the pharmacokinetic properties of BUP and/or its active ingredients.

BUP is extensively distributed and both HCl-BUP and its active metabolites bind to plasma proteins (84% BUP, 77% hydroxybupropion and 42% threohydroxybupropion) in proportions that are not considered excessively high and do not suppose a clinically relevant problem.[51] All are excreted through breast milk[52, 53] and are capable of crossing the blood-brain barrier and placental barrier.

The Tmax is one and a half hours for the IR formulation, three hours for the SR and five hours for the XL/XR formulation.[31] The Cmax, after a single dose of 150 mg of SR in healthy adult males, was 143 ng/ml in one study and 91 ng/ml in another. The Tmax of hydroxybupropion, after a single dose of the SR formulation, was six hours.[11, 31]

When it is administered in the morning, the plasma concentrations of BUP XL/XR are lower during the afternoon hours.[22] After stable doses are reached, it has been demonstrated that the XL/XR formulation is bioequivalent to the IR formula administered three times a day, or to the SR one administered twice a day[31] as well as the areas under the curve. However, it has the advantage that there is only one daily peak with the XL/XR formulation while there are two with the SR and three with the IR.[54]

Interactions

CYP2B6 inhibitor drugs, such as clopidogrel and ticlopidine (antiplatelet) and valproate, may have an effect of reducing the proportion between hydroxybupropion and bupropion, observing up to 68% reduction in the case of clopidogrel and up to 90% in the case of ticlopidine. Due to the important contribution of hydroxybupropion in the clinical efficacy of BUP, it may be affected by this interaction.[55] Furthermore, CYP2B6 is an enzyme that is inducible via agents such as tobacco, alcohol, phenobarbital and carbamazepine. Its concurrent use may induce concomitant increase of the production of hydroxybupropion.[11] Therefore, the levels of BUP and its active metabolites may be reduced or elevated when combined with inductor or inhibitor substances of CYP2B6, respectively, which may entail changes in the efficacy or tolerability of BUP.

BUP is a potent inhibitor of CYP2D6, which may give rise to the reduction of elimination of drugs metabolized by this isoenzyme.[56] An *in vivo* study that used dextromethorphan as a probe drug demonstrated the inhibition of CYP2D6 exerted by BUP. Administered together, a significant increase was observed in the dextromethorfan/ dextrorfan proportion.[11] A study on the pharmacokinetic interaction of HCl-BUP at multiple doses and desipramine monodosis in 15 healthy volunteers showed that its combined administration produces a desipramine concentration five times greater than when it is administered alone. This demonstrates the inhibition of CYP2D6 exercised by BUP and its active metabolites.[11] Among the drugs metabolized by CYP2D6 are the antidepressants selective serotonin reuptake inhibitors (SSRI) and the tricyclics, beta-blockers, the antiarrhythmic drugs propafenone and flecainide and the antipsychotics risperidone and thioridazine. Concomitant treatment of BUP with drugs that are predominantly metabolized by CYP2D6 should be initiated at the lowest doses of both

Table 2 Interaction of drugs with Bupropion

Inhibitors of CYP2B6 (they decrease plasma levels of bupropion)	
Platelet inhibitors	Clopidogrel, Ticlopidine
Inductors of CYP2B6 (they increase plasma levels of bupropion)	
Tobacco	
Alcohol	
Anti-seizures	Phenobarbital, Carbamazepine
Others drugs metabolized by CYP2B6	
Tricyclic antidepressants	Imipramine, Amitriptyline, Clomipramine, Doxepin, Lofepramine, Nortriptyline, Trimipramine
Tetracyclic antidepressants	Desipramine, Maprotiline, Mianserine
Beta-blockers	Metopropol
Antiarrhythmic	Propafenone, Flecainide
Antipsychotics	Risperidone, Thioridazine
Drugs that potentially reduce the seizure threshold	
Costicosteroids	Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Paramethasone, Prednisolone, Fludocortisone, Prednisone, Triamcinolone
Antimalarial agents	Chloroquine, Quinine, Mefloquine, Halofantrine, Primaquine
Antipsychotics	Chlorpromazine, Fluphenazine, Levomepromazine, Perphenazine, Pipotiazine, Thioproperazine, Thioridazine, Trifluoperazine, Haloperidol, Zuclopenthixol, Sulpiride, Tiapride, Loxapine, Pimozide
Quinolones	
Antihistamine sedatives	
Anti-asthmatics	Theophylline
Analgesics	Tramadol
Monoamine Oxidase Inhibitors	Tranylcypromine, moclobemide (RIMA) selegiline, rasagiline
Drugs that potentially reduce the seizure threshold	
Levodopa	
Amantadine	

drugs, always evaluating the risks-benefits of the concomitant administration of these drugs with BUP.

Caution should be taken when prescribing BUP together with drugs having known potential to decrease seizure threshold (antidepressants, antimalarial drugs, antipsychotics, quinolones, antihistamine sedatives, systemic corticosteroids, theophylline and tramadol).[11]

The combined use of BUP with MAOIs is contraindicated since MAOI A and B inhibit degradation of amines, increasing the noradrenergic and dopaminergic neuronal transmission. The combination of MAOIs and BUP may lead to overstimulation of these catecholaminergic systems and consequently give rise to side effects. Treatment should not be initiated with BUP until 14 days after irreversible suspension of MAOI or 24 hours after reversible suspension of an MAOI.[11]

Due to its metabolism via cytochrome P450-2B6, the combined administration of other drugs affecting this isoenzyme (cyclophosphamide, ifosfamide, orphenadrine, ticlopidine, clopidogrel) may give rise to reduced plasma concentrations of hydroxybupropion, and high levels of BUP, although the real clinical consequences of these interactions are unknown.[11]

The administration of BUP to patients who are receiving treatment with levodopa or amantadine should be performed with care, since a greater incidence of side effects (nausea, vomiting, and secondary neuropsychiatric effects) has been described.[11]

Interactions between BUP and alcohol intake have not been identified.[57] However, neuropsychiatric side effects or reduction of tolerability to alcohol have been recorded during treatment with BUP.[57] Therefore, alcohol consumption should be minimized or completely suspended. BUP should not be administered in patients who are in the process of abrupt alcohol abstinence. No clinical and pharmacokinetic studies have been conducted on the interaction between benzodiazepines and BUP. However, the sedative effect of diazepam was reduced when administered in combination with BUP in comparison to when administered alone.[21, 58] A summary of the interactions is shown in table 2.

Synthesis of the chemical and pharmacological characteristics

BUP is a monocyclic phenylbutylamine of the aminoketone group, a dual mechanism antidepressant that inhibits neuronal uptake of NE and DA that does not have a significant effect on other transporters or other neurotransmission systems or specific affinity for post-synaptic histaminergic, muscarinic, alpha or beta adrenergic, serotoninergic receptors, although it acts as a non-competitive antagonist of some nicotonic receptors. It does

not have an amphetamine type stimulating activity as it does not increase DA release.

There are several symptoms of depression that seem to be intensely associated with dopaminergic and noradrenergic mechanisms and circuits. Among these are depressive mood, motivation, capacity to experience pleasure (anhedonia), response to reward and loss of interest. The principal structures involved would be the mesocorticolimbic circuit, which innervates its limbic structures such as the nucleus accumbens, amygdala and the ventral hippocampus, as well as the cortical structures such as the prefrontal cortex. BUP, on increasing the DA tone, could have a beneficial effect on anhedonia, lack of motivation and energy. It has even been suggested that the antidepressant effect of BUP would depend on the DA levels in the n. accumbens. On the other hand, the increase in catecholaminergic activity in dorsolateral prefrontal cortex would improve psychic fatigue while its increase in the striate and/or cerebellum would improve physical fatigue.

Within the pharmacokinetic characteristics of BUP, in the modified release formulation (XR), we would stress its hepatic metabolism by the P450 (CYP) 2B6 cytochrome to form an active metabolite, hydroxybupropion. The hydroxybupropion could be responsible for most of its clinical effects.

Among its interactions, we would stress those existing with CYP2B6 inhibitors, such as clopidogrel, ticlopidine and valproate that may reduce the proportion between hydroxybupropion and bupropion. Tobacco, alcohol, phenobarbital and carbamazepine may increase the proportion of hydroxybupropion. On its part, BUP, which is an inhibitor of CYP2D6, may give rise to reduced elimination of drugs metabolized by this isoenzyme (SSRI, ATC, beta-blockers, antiarrhythmic propafenone, risperidone). BUP should be prescribed with precaution when administered together with drugs of recognized potential to decrease seizure threshold, inhibitors of P450-2B6, antiparkinsonians, benzodiazepines and alcohol.

In conclusion, BUP is a potent dual DA/NE acting antidepressant mechanism with specific action on anhedonia, motivation and energy that complete the existing therapeutic armamentarium.

CLINICAL EFFICACY

The clinical efficacy of BUP has been studied in its three formulations compared to placebo, in hospitalized and outpatients, adults and the elderly, versus other antidepressant drugs, BUP showing equal or greater efficacy than the others, and, in general, good tolerability. The therapeutic clinical trials have used different doses, going from 100 mg/day up to 600 mg/day. This review distinguishes two groups of BUP doses in the clinical trials to summarize its clinical efficacy: dose up to 300 mg and higher doses (450 mg/600 mg). Since the maximum approved dose in Spain is 300 mg/day, the results will be described separately. Furthermore, a presentation will be made of the studies according to the BUP formulation used.

Immediate (IR) or sustained (SR) release bupropion

Dose up to 300 mg

In a multicenter, double-blind study, 224 patients with MDD were randomized into two groups to receive BUP up to 300 mg/day, or placebo for 6 weeks. A total of 216 patients were included in the efficacy analysis, which was evaluated on days 21, 28, 35 and 42 of the study using the Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression-Self Reported (CGI-S). BUP showed a significantly higher clinical efficacy than the placebo after day 28 in the combined analysis of the centers, measured with the 3 scales. This result remained significant during the rest of the study. Furthermore, in the end of the treatment evaluation conducted, 51% of the patients in the BUP group were classified as responders (reduction of the score on the HAM-D scale $\geq$ 50%) compared to 34% of the patients in the placebo group (p=0.01).[59]

Reimherr et al. reported on a multicenter clinical trial of 8 weeks duration in which treatment was randomly assigned to 362 patients: 121 patients received BUP at a dose of 150 mg/day, 120 patients received BUP IR 300 mg/day and 121 patients received placebo. BUP, at both doses, was shown to be significantly more effective than the placebo in the treatment of MDD. The evaluation of the efficacy of BUP versus the placebo with the HAM-D, CGI-S and Clinical Global Impression of Improvement (CGI-I) scales found significant differences ($p\leq0.05$; $p\leq0.05$ and $p\leq0.01$, respectively).[60]

After the development of the SR formulation, Kavoussi et al. found a similar efficacy for BUP SR and sertraline in 248 outpatients, with less frequency of some adverse effects (orgasm dysfunction, nauseas, diarrhea, somnolence and sweating) for BUP versus sertraline ($p\leq0.01$).[61] Kennedy did not observe significant differences in relationship to antidepressive efficacy with BUP SR compared to paroxetine in 141 patients with MDD.[62] Weihs et al. also observed similar efficacy of BUP compared to paroxetine in the results of all the antidepressive efficacy evaluation scales during the six weeks of the study duration.[63] In another study, Weihs et al. also found that BUP SR was effective in the

treatment of MDD in patients with recurrent episodes who underwent prolonged treatment for 44 weeks, after an initial treatment of 8 weeks. They detected significant differences in favor of BUP versus placebo in the prevention of the recurrence of the depressive episode ($p<0.05$) and pointed out the good tolerability to the drug.[64] It has been shown to be equally effective in atypical and bipolar depression[65] and has been shown to improve the quality of life of elderly patients with MDD.[66]

Efficacy of BUP SR was demonstrated in a meta-analysis that included 7 clinical trials with 732 patients randomized for treatment with BUP versus 339 with fluoxetine, 343 with sertraline and 49 with paroxetine. Four studies included control with placebo group (512 patients). Although only two of the trials included had therapeutic doses restricted to 300 mg, mean doses less than 300 mg/day were reached in all the trials. BUP showed a similar efficacy to the rest of the drugs that was, in every case, statistically superior to placebo ($p<0.01$). Furthermore, the odds ratio of remission of the symptoms after treatment was similar for both therapeutic groups and significantly superior to the placebo ($p<0.01$).[67]

Dose Superior to 300 mg

The IR formulation has been shown to be effective in treatments of MDD versus placebo in hospitalized patients at a dose of 300 to 600 mg/day, already in the third week. BUP was shown to be effective in reducing depressive and anxious symptoms, evaluated with the HAM-D, *Hamilton Rating Scale for Anxiety* (HAM-A), CGI-S and CGI-I scales, specifically in older patients and those with more serious episodes.[68, 69] Another study conducted in 115 outpatients compared BUP at a dose of 225 to 450 mg/day (mean 333 mg/day) with nortriptyline at a dose of 75 to 150 mg/day (mean 111 mg/day), and observed equal efficacy and greater safety for BUP.[70] In addition, BUP showed its efficacy and safety compared to amitriptyline in outpatients, with a better safety profile for BUP.[13, 14] Compared to imipramine, 63 patients between 55 and 80 years of age were randomly assigned to 4 treatment groups: 18 patients at a low dose of BUP (150 mg/day), 18 patients at a high dose of BUP (300 – 450 mg/Bay), 18 patients to imipramine (25 mg/day) and 9 patients to placebo. At 14 days of treatment, there was similar efficacy in all the groups in active treatment, this being significantly superior to placebo. This efficacy was maintained until the end of the study ($p<0.05$). The group receiving high doses of BUP showed a significantly higher response than the others after only 7 days of treatment. The incidence of adverse effects of BUP was comparable to placebo. More information is given on this study in point 2.7.1 (Special populations. The elderly).[18] In addition, Feighner et al. demonstrated the efficacy of BUP IR compared to doxepin[17] and fluoxetine,[71] finding comparable reductions in the scores on the HAM-D and HAM-A scales in both trials between the reference drug and BUP.

The SR formulation was also compared at elevated doses against the placebo and other antidepressive treatments.[72-75] In one randomized, double blind study on BUP SR versus sertraline and compared with placebo, only BUP SR achieved significant reductions that were superior to placebo on the HAM-D and CGI-S scales at the end of the study ($p<0.05$).[72] Furthermore, compared to fluoxetine, both active treatments obtained results that were significantly superior to the placebo on all the scales.[73] Papakostas (2007) found similar efficacy between BUP-SR and SSRI in a meta-analysis of seven randomized clinical trials, no significant differences being observed regarding action onset time and first remission of symptoms between both groups.[76]

BUP SR has also demonstrated efficacy in monotherapy in patients resistant to previous anti-depressive treatment, or with inadequate response to treatment.[77, 78]

Bupropion xl/xr modified release

BUP XL/XR is the formulation for a single daily administration approved in 2003 (USA) and 2007 (Europe) on the basis of its bioequivalence with the two previous formulations,[11, 54] as well as new clinical data. Granger et al. indicated the importance of having a single daily administration formulation when they observed that in most of the 527 patients surveyed who were under treatment with BUP IR or SR, specific failures to take the antidepressants were due to simple forgetfulness. The results also suggested that 77% of the patients under treatment with the SR formulation (administration 2 times a day) and 94% of those with the IR formulation (3 times a day) were interested in having a single daily dose presentation.[79] As is well-known, reduction in the frequency of daily dosage can improve antidepressive treatment compliance. This, in turn, may have a favorable repercussion on the relief of the symptoms, improvement of quality of life and cost reduction.

Doses of up to 300 mg

Efficacy, safety and tolerability of BUP XL at a dosage of 150 a 300 mg/day were demonstrated in a randomized clinical trial versus placebo, controlled with venlafaxine XR (75 to 150 mg/day) and placebo. A total of 571 patients received at least one dose of the medication and 485 completed the treatment phase. Clinical efficacy was evaluated with the MADRS, CGI-I, CGI-S and HAM-A scales for 8 weeks while safety was evaluated through the

collection of adverse events and clinical variables from the usual medical visit. Both drugs showed comparable antidepressive efficacy and, in both cases, they were significantly superior to placebo in all the measurements, with a similar rate of adverse events which, in every case, were mild.[80] However, in another clinical trial with an identical design and comparators, no significant differences were found in the anti-depressive effect demonstrated by BUP XL/XR and placebo (results with a 95% confidence interval).[81] Another multicenter, randomized, double-blind, parallel group clinical trial compared a flexible dose of BUP XL/XR (150-300 mg) versus placebo, during 10 weeks of treatment and a follow-up phase to evaluate safety in 418 patients ≥65 years of age. The principal efficacy endpoint was defined as mean change in this score on the MADRS scale between the baseline visit and the final treatment visit at week 10. According to the study protocol, the differences in the score between both groups would be analyzed using the ANCOVA test. However, the necessary assumptions to carry out this test (equal regression slopes for both treatment groups) were not fulfilled, which is why the differences detected were not significant. Thus, a nonparametric ANCOVA test was performed and its result showed a significant improvement in the depressive symptoms in the treatment group with BUP XL/XR compared to the placebo group (p=0.03). The change in the total MADRS scale from the baseline visit to week 10 was -15.0 points for the BUP XL/XR treated group and -11.0 points for the placebo group. After, a regression analysis was performed. It confirmed that the reduction of the score on the MADRS scale was significantly greater with BUP XL/XR when compared with the placebo group in week 10 (p=0.021). The rest of the secondary efficacy variables in the study were significantly greater for BUP XL/XR than for its comparator. More information on this study is provided in point 2.7.1 (Special populations: The elderly).[82]

Dose Superior to 300 mg

The efficacy of BUP XL/XR versus placebo and other antidepressants has been demonstrated,. It demonstrated, as an advantage, a good safety and tolerability profile. Jefferson et al. compared the efficacy of BUP XL/XR versus placebo-treated group for 8 weeks of treatment and 10 weeks of total duration of the study that included one previous week of screening and a subsequent week of follow-up to evaluate safety. BUP XL/XR was shown to provide a significant improvement in the mean score on the IDS-IVR-30 scale (*Inventory of Depressive Symptomatology-Self Report*) compared to placebo in the evaluations corresponding to weeks 1, 2 and 8 (p<0.05). A significant reduction (p<0.001) was also observed in the mean score on the IDS-C-30 scale (*Inventory of Depressive Symptomatology-Clinician-Rated*) at the end of the study. The response rates of the IDS-C-30 and CGI-I were significantly better for the BUP XL/XR treated group at week 8: 50% of response with BUP and 35% with placebo for the IDS-C-30 (p=0.009) and 53% in BUP *vs* 38% in placebo for the CGI-I (p=0.006).[83]

Several studies have included the XL/XR formulation with other antidepressant drugs. In this way, in 2006 Clayton et al. published a clinical trial in patients with severe MDD treated over 8 weeks that compared, as the primary efficacy objective, the mean change in score on the HAM-D-17 scale produced by BUP XL/XR(n=276) compared to escitalopram (n=281). The study was controlled with a third group of patients treated with placebo (n=273). The efficacy evaluation made in the final treatment visit (week 8) showed improvement in the score obtained in all the treatment groups. However, it did not show a statistically significant difference between BUP and escitalopram (p=0.533).[84] Regarding venlafaxine XR and within the secondary objectives of their study, in 342 outpatients diagnosed of depression (251 of whom were considered to be sexually active) Thase et al. observed a comparable improvement between venlafaxine XR and BUP XL/XR in the score obtained on the HAM-D-17 scale over the 12 weeks of treatment. In regards to compliance, 56% of all the randomized patients completed the study (58% in the BUP XL/XR treated group and 54% in the venlafaxine XR treated group), 11% of the patients treated with venlafaxine XR and 6% of those treated with BUP XL/XR prematurely abandoned treatment due to the appearance of adverse events. In regards to losses to follow-up, these occurred in 20% of the venlafaxine XR treated patients and in 14% of the BUP XL/XR treated patients.[85]

Clinical efficacy in specific symptoms: lack of motivation, energy and fatigue

Depressed patients frequently have symptoms of decreased energy, pleasure and interest. Of these, 56% also have depressed mood (sensation of sadness), sadness, and in patients over 60 years, 99% of the patients show decreased interest in work and in other activities, and 97% decreased energy.[73]

Dose Superior to 300 mg

Jefferson et al. conducted a 10-week randomized, double blind, placebo-controlled study with BUP XL/XR in 260 patients with criteria of MDD and decreased energy, perception of pleasure and decreased interest. BUP XL/XR was shown to be significantly superior to placebo in regards to most of the response and remission

measurements. Symptoms directly related with the objective of the study, that is, energy, pleasure, interest, insomnia and anxiety, were evaluated independently. In the first 4 symptoms, the results were significantly better with BUP XL/XR at the end of the treatment (8 weeks) (IDS-IVR-30 p=0.007; IDS-C-30 p<0.001). BUP XL/XR also showed a significantly greater decrease in the global scores of the IDS-IVR-30 scale at weeks 1, 2 and 8 (p<0.05) and in the global score of the IDS-C-30 scale in the evaluations corresponding to weeks 1, 2, 4 and 6 (p<0.05), as well as in the final treatment visit (week 8) (p<0.001). In relationship to anxiety, the difference between both groups was not statistically significant.[83]

Clinical efficacy in patients who do not respond to a previous treatment. Switch / augmentation

Since 1994, Ferguson et al. have suggested the therapeutic utility of BUP as a substitution treatment after absence of response to treatment with tricyclic antidepressants.[86]

Dose of up to 300 mg

Several studies have shown the efficacy of BUP combined with other drugs as an augmentation strategy. Apter et al. observed the efficacy of the combined treatment of BUP with nortriptyline in four patients with depression refractory to monotherapy or other therapeutic combinations for at least 6 weeks. Even though the cases are not controlled, experience regarding the efficacy of this combination, duration of the antidepressant effects of the treatment and profile of safety were considered to be good.[87] DeBattista showed remission of the symptoms in 54% of the patients studied when BUP was combined with venlafaxine after failure to therapeutic response in monotherapy with SSRIs (fluoxetine, paroxetine, sertraline and venlafaxine).[88] This combination was also shown to be effective in 56% of the patients of the study made by Spier. It was also well tolerated, even in geriatric patients and those having a delicate medical condition.[89]

Dose Superior to 300 mg

Ferguson et al. conducted a study on 41 patients diagnosed of depression without response to tricyclic antidepressants. At the end of 8 weeks of open treatment with BUP IR, 49% of the patients (95% CI 33-65%) responded to treatment: a reduction of ≥50% of the score on the HAM-D scale in the final treatment visit (week 8) regarding the baseline visit. Furthermore, the reduction in the score of all these scales evaluated (HAM-D, HAM-A, CGI-S, CGI-I) between the final treatment visit and the baseline visit was significant (p<0.0001).[86] Fava et al. obtained 60% total or partial response in an open study in 29 BUP treated patients during 8 weeks who had not responded previously to fluoxetine.[77] The STAR*D study demonstrated the clinical efficacy of BUP in cases of inefficacy of the treatment or previous intolerance to citalopram. They incorporated 4041 patients into the study, 3671 of whom initiated a first treatment phase with citalopram.[78] A total of 727 patients diagnosed of MDD who did not have associated psychotic symptoms were randomly assigned to three groups to receive BUP SR (n=239), sertraline (n=238) or venlafaxine XR (n=250). The percentages of remission, reduction, tolerability and safety were similar for all the drugs. Approximately one out of every four patients who switched from citalopram to another antidepressant achieved complete remission of their depression symptoms. Any of these drugs can be considered for their utility and their side effects should be taken into account for their choice. [90] One more recent study in this group of patients analyzed the predictive value of the clinical, demographical endpoints and the characteristics of the initial treatment in the response to a second antidepressant in monotherapy (BUP *vs* sertraline or venlafaxine). It was found that these variables had little value for the recommendation of one medication over another.[91]

Also in relationship with the STAR*D study, Trivedi et al. compared BUP SR with buspirone as an added drug in patients without response or with intolerability to citalopram (n=565). Those patients treated with citalopram and BUP SR followed adherence to the treatment for a longer time (10.2 weeks) compared with the group that received citalopram and buspirone (9.2 weeks) (p=0.01). Significant differences were found in favor of the combination of citalopram + BUP SR in the reduction of the QIDS-SR-16 scores (*Quick Inventory of Depressive Symptomatology-Self-Report*) from the onset to the end of the study (p<0.04). In addition, the scores in this questionnaire were significantly lower in the citalopram + BUP SR group at the end of the study (p<0.02) and also showed lower rates of discontinuation due to intolerability (p<0.001).[92]

Bodkin et al. conducted a retrospective study that included 27 patients previously treated with SSRIs or BUP for a mean of 19.3 ±16.7 months and who had partial benefits or incomplete recovery after the monotherapy. Instead of replacing the antidepressant, they added BUP in the case of the SSRI and on the contrary, SSRI to those previously treated with BUP monotherapy, for a mean of 11.1±14.3 months. In 70.4% of the patients, it was considered that the effect of the combined therapy had been beneficial. They found some significant differences regarding associated symptoms (improvement of energy, concentration and cognition for BUP, and anxiety and panic for SSRI).[93] Papakostas suggested

the efficacy of the combination of duloxetine and BUP in the treatment of MDD resistant to the initial treatment with either of the two drugs in the clinical trial limited by the sample size (10 patients). Three patients achieved complete remission of the symptoms, while there was partial remission with mild side effects in six.[94]

Effect on the cognitive function in patients with MDD

Patients with depressive disorders more frequently have various alterations of the neurocognitive functions. Recently, different studies demonstrated that, in spite of treatment with new generation drugs, residual attention, executive function and information processing speed deficits may persist, even after obtaining clinical improvement.

Dose up to 300 mg

Herrera et al., in 12 depressed patients, observed that some cognitive alterations, such as poor visual memory or slow down of the cognitive processing, could be predictors of a good response to treatment with BUP.[95] Gualtieri, in a naturalistic study conducted in 81 outpatients, aged 18 to 65 years, diagnosed of unipolar, non-psychotic major depressive disorder without associated neurocognitive disorders, analyzed the level of cognitive performance reached after the use of the following drugs: bupropion (n=27), venlafaxine (n=27), and SSRI (n=27), until completing a total of seven active ingredients. The study included 27 control patients who were selected by matching of the variables for age, race and gender, and who had a normal health condition, with no psychiatric, neurological or cognitive on-going diseases or backgrounds of them and who were not receiving any central nervous system activator treatment.

Based on the results of this study, it was possible to verify that in comparison with the registries obtained in the control group, the score obtained in the SSRI treated patient group was lower in the psychomotor speed test, cognitive flexibility and response time. In the venlafaxine-treated patient group, the score obtained was lower for the measurement of the reaction time. In the bupropion-treated patient group, no differences were found regarding the values of the control group in any of the cognitive domains evaluated (verbal memory, visual memory, finger tapping test, capacity to identify symbols, Stroop color-word test, floating attention test and performance test and *Conner's continuous performance test*.[96]

Some reviews suggest the possibility that BUP is a therapeutic alternative in adults with attention deficit hyperactivity disorder and major depression on the basis of the available clinical evidence.[97]

Effect on anxiety associated to depression

Anxiety symptoms are frequently associated to MDD, which gives rise to greater severity, greater general functional disk capacity in addition to greater risk of suicide, and usually worse therapeutic results. It has been suggested that those antidepressants indicated in anxiety disorders (e.g. sertraline or paroxetine) could cause a greater anxiolytic effect in these patients.

Dose up to 300 mg

Rush et al. compared the anxiolytic and antidepressant effect on the reduction in remission of symptoms in a retrospective observational study that grouped patients according to whether they received BUP SR or sertraline. Both drugs were shown to be equally effective in the reduction of depressive and anxious symptoms. No statistically significant differences were observed in the scores obtained on the HAM-D and HAM-A scales used for their evaluation at any time of the study. During the 16 weeks of the study, no differences were found between the baseline levels of anxiety and the remission rates with either of the two treatments used. Therefore, the choice of BUP SR was shown to be equally effective as that of sertraline in cases of anxiety associated to MDD, since the baseline levels of anxiety were not related with antidepressant efficacy nor were they associated with differences in response to each active ingredient. Therefore, the authors concluded that the presence of anxious symptoms should not affect the choice of antidepressant.[98]

Dose Superior to 300 mg

In addition, the meta-analysis of Papakostas (2008) found the same anxiolytic efficacy in relationship to MDD between the SSRIs and BUP. They did not detect significant differences in treatment time to achieving anxiolytic effect or in the proportion of patients who experienced residual anxious symptoms. These results seem to contradict the perception of some clinicians regarding the superiority of the SSRIs in the treatment of MDD with a strong anxious component.[99]

Special populations

Elderly patients

BUP has demonstrated its anti-depressive effect in elderly patients, with the tolerability and high safety profile,

improving the patient's quality of life with limited cardiovascular and alert state effects. Fabre found that the half-life of BUP and its metabolites in elderly patients was longer than that of young subjects.[68] By 1986, in the review by Bryant, the utility of BUP was suggested in elderly patients due to its combination of efficacy and safety.[100]

Dose up to 300 mg

Fortner demonstrated the efficacy of BUP in improving the global quality of life in elderly patients regarding the previous evaluations at the onset of treatment, in an 8-week study performed in patients with MDD and one or more comorbidities: diabetes, congestive heart failure, irritable bowel syndrome, etc. The quality of life was measured with the SF-36 scales for mental health (*Short Form Assessed Health-Related Quality Of Life*) ($p<0.03$), CGI-S ($p<0.0001$) and the HAM-D-17 ($p<0.0001$), as well as social functioning ($p<0.0006$). Improvement was also found in aspects such as vitality ($p<0.03$), feelings of sadness ($p<0.0001$), guilty feelings ($p<0.01$), work and activities ($p<0.001$), hypochondria ($p<0.02$), and insomnia ($p<0.01$).[101] In addition, BUP has been shown to be effective compared to placebo[102] and paroxetine[63] in subsequent studies conducted in elderly patients. Recently, Hewett et al. demonstrated its efficacy versus placebo and controlled with venlanfaxine in elderly patients.[82]

Dose Superior to 300 mg

Branconnier demonstrated in elderly patients that the antidepressant efficacy of BUP was comparable to imipramine. Higher doses of BUP showed a faster onset of its effect than lower doses and a more important anxiolytic effect. BUP had similar side effects as the placebo and, on the contrary to imipramine, no anticholinergic effects were observed.[18]

Hepatic disease

BUP and its active metabolites are principally metabolized in the liver. No significant differences were observed regarding its bioavailability in healthy volunteers and in patients with mild to moderate hepatic cirrhosis. However, greater variation was observed in the drug plasma levels, a significant increase in plasma elimination half-life and time to maximum concentration in plasma, as well as reduced kidney elimination in those volunteers with severe hepatic cirrhosis compared with healthy volunteers.[19, 103] Therefore, precaution is recommended for its use, decreasing the administration frequency and/or reducing the dose in patients with mild to moderate liver failure.[31] BUP XR/XL is contraindicated in patients with severe hepatic cirrhosis.[104]

Kidney failure

The metabolites of BUP are principally excreted through the kidney. The treatment of patients with kidney failure should be initiated at reduced dose since there may be a greater accumulation of BUP metabolites in these patients. An open study in patients with end-stage kidney disease indicates that the concentration of the active metabolites in plasma may duplicate those of individuals with conserved retinal function. Hemodialysis decreases the concentrations of BUP, hydroxybupropion and erythrobupropion, by 13%, 4% and 17%, respectively after 4 hours of hemodialysis. In these patients, the side effects should be carefully monitored (insomnia, dry mouth, seizures) as they could indicate an elevated plasma concentration of BUP. The recommended dose for these patients is 150 mg/day.[31, 104]

Pregnancy

Its safety has not been demonstrated in pregnancy and breast-feeding. However, data have been obtained on possible tetratogenicity compared with paroxetine and other drugs. These data do not reveal a greater incidence of congenital malformations when the patients are exposed to treatment with BUP during the first quarter of pregnancy.[105, 106]

Synthesis of the efficacy of bupropion

Without detriment to the demonstrated efficacy of BUP based on the numerous controlled clinical trials and meta-analysis on MDD, from a clinical point of view, it is of maximum interest to have a dopaminergic antidepressant drug because low levels of 5-HT, NE and DA seem to be associated with depressed mood state, defining symptom of MDD. Furthermore, all antidepressant drugs that increase the levels of these neurotransmitters produce a clinical improvement in depressed mood. Other important symptoms in depressive disorders such as decreased motivation, decreased capacity of experiencing pleasure (anhedonia), of response to reward, loss of interest, decreased attention and concentration, etc. have been associated to a decrease in dopaminergic activity while an increase has been observed in motivation in the depressed patient, cognitive improvement and reduction of anhedonia when the dopaminergic activity is increased.

Therefore, it is a very interesting drug, especially in those cases of MDD with clinical expression of psychomotor inhibition, cognitive affectation and/or physical or

intellectual fatigue (areas of the brain such as the striatum and/or cerebellum that control the motor functions may be involved in physical fatigue and cortical areas may be related, in turn, with psychic fatigue), that is, in inhibited endogenous depressions. The possibilities of association are many, this adding a strategic value to the formulating of augmentation or substitution treatments in depression refractory to other treatments.

Of special interest is its efficacy and good tolerability and safety profile in addition to the possibility of using it in elderly persons. Its ease of management due to the variety of existing presentations contributes to an increase in treatment compliance and therefore its efficacy.

Thus, BUP is a useful therapeutic alternative in the treatment of depressive patients. On the one hand, it has an activator profile, very desirable in patients with predominantly inhibitory symptoms. On the other hand, its tolerability, with absence of anticholinergic effects and interference with sexual function, may favor treatment adherence. Some other differential aspects, such as potentially lower dangerousness to provoke change in bipolar patients, add value to its availability.

SAFETY

The most frequently found adverse events related to the use of antidepressant medication are: constipation, diarrhea, seizures, headache, insomnia, nausea, sexual dysfunction and somnolence.[107] Nauseas and vomiting are the adverse events most commonly related with discontinuation of treatment in the studies on efficacy. Most second-generation antidepressants have a very similar safety profile, with some differences regarding the incidence of specific adverse events as those described in the following.

Adverse events described with bupropion

Due to the high number of patients treated with BUP worldwide (more than 15 million have been estimated in the USA alone), a profile of adverse reactions associated to BUP has been established.[19] In a review of three placebo-controlled studies on BUP SR, Settle et al. identified that the most frequent adverse reactions (occurring in ≥ 5% of the patients and more frequently than with the placebo) were headache, mouth dryness, nauseas, constipation, insomnia and dizziness.[108]

From the clinical point of view, it is possible to observe exanthema-type allergic reactions, pruritus and rash and rarely anaphylactic/anaphylactoid reactions associated to the use of BUP.[109]

Comparison with placebo

Several studies have demonstrated the safety of BUP compared to placebo, the number of adverse events not being much higher, these being mild in general, and variations of clinical and laboratory parameters which, mostly, did not show statistically significant differences in regards to the placebo.

Lineberry et al., in 224 outpatients treated with BUP IR at fixed doses of 300 mg, only found four adverse events that occurred in more than 5% of the individuals of the group: headache (38% BUP *vs* 26% placebo); insomnia (23% BUP *vs* 7% placebo); dizziness (15% BUP *vs* 6% placebo) and nauseas (13% BUP *vs* 10% placebo). None of these differences was statistically significant.[59]

Settle et al. compared BUP SR against placebo in regards to a series of parameters that included adverse events presented, changes in the physical parameters during the clinical examination and changes in laboratory values. A total of 11% of the patients being treated with placebo prematurely dropped out of the treatment compared to 7% of the patients being treated with BUP SR ($p < 0.05$). The reasons for dropout were attributed to poor response to treatment or deterioration of the initial symptoms. Furthermore, 7% of the patients in the BUP SR group dropped out of treatment prematurely due to adverse events compared to 4% in the placebo group ($p < 0.05$). Adverse events associated with dropout from treatment were: exanthema, nausea, anxiety, headache and agitation. In those subjects who completed the treatment, the adverse event observed most frequently in both groups was headache, this presentation difference not being statistically significant between both groups. The sensation of dry mouth and insomnia occurred more frequently in the BUP-treated group in regards to the placebo group ($p < 0.05$). There were no significant changes in systolic or diastolic blood pressure, pulse rate, or in the laboratory values for either of the two groups.[108]

Modell et al. analyzed the adverse events in the BUP XL/XR treated group versus placebo. The adverse events observed most frequently were: sensation of dry mouth (26% BUP *vs* 15% placebo); nauseas (13% BUP *vs* 8% placebo), constipation (9% BUP *vs* 2% placebo) and flatulence (6% BUP *vs* 3% placebo). These differences were not statistically significant. A small increase, although statistically significant, was observed in heart rate with a mean increase of 1.6 beats per minute ($p<0.001$) and elevation of systolic blood pressure of 1.2 mm Hg ($p=0.013$) in the BUP-treated group.[110]

Comparison with tricyclic antidepressants

One study that compared BUP and nortriptyline administered for 6 weeks in 115 patients with moderate

to severe MDD showed that the patients treated with nortriptyline had a significantly higher rate of somnolence (14% nortriptyline, 3% BUP; p<0.05); tachycardia (14% nortriptyline, 3% BUP; p<0.05) and sensation of dry mouth (61.4% nortriptyline *vs* 34.5% BUP, p<0.001). In the BUP treated patients, there was a higher incidence of headache (22.4%), constipation (17.2%), nauseas (10.3%), dizziness (10.3%) and insomnia (10.5%), although without significant differences regarding nortriptyline in any of them.[70]

Comparison with selective serotonin reuptake inhibitors (SSRI)

Thase et al., in a meta-analysis of seven randomized clinical trials, observed that identical percentages of individuals (7%) suspended treatment due to the adverse events presented in the BUP treated group and those in the SSRI-treated group.[67] The incidence of adverse events is shown in table 3.

Kavoussi et al., on comparing BUP SR and sertraline, found that headache was the most frequent adverse event in both treatment groups (34% BUP, 32% sertraline). However, significantly more patients treated with sertraline had nauseas (30% sertraline *vs* 10% BUP SR), diarrhea (22% sertraline *vs* 3% BUP SR), somnolence (13% sertraline *vs* 2% BUP SR) and sweating (10% sertraline *vs* 2% BUP SR).[61] Similarly, Croft et al. observed a significantly higher incidence of adverse events (nauseas, diarrhea, insomnia and somnolence; p<0.005) in patients treated with sertraline then in those treated with BUP-SR.[74]

Other studies have found statistically significant differences in favor of BUP in the incidence of adverse events, specifically somnolence, when compared with paroxetine[63] and citalopram,[84] while significant differences were not found between BUP and trazodone.[111]

Comparison with serotonin–norepinephrine reuptake inhibitors (SNRIs)

In a study in which BUP was compared with venlafaxine XR,[85] the adverse events that were most frequently observed with the BUP group, and that also caused premature dropout from treatment were vertigo/dizziness (1%) and anxiety (1%) (Table 4). A total of 11% of the venlafaxine-treated group were withdrawn due to adverse events while only 6% of the BUP group were withdrawn for the same reason (p n.s.). In addition, as commented further below, BUP XL demonstrated a significantly more favorable profile regarding sexual function than venlafaxine XR.

Sexual dysfunction

Safety of bupropion within the sexual dysfunction setting

Sexual dysfunction occurs frequently in patients with major depressive disorder and may be caused by the depressive picture or as a side effect of antidepressant treatment. Sexual dysfunction secondary to treatment may affect practically all of the sexual activity spheres: Sexual desire, erection, ejaculation and orgasm, causing lack of satisfaction and general sexual dysfunction.

Several randomized clinical trials in meta-analyses indicate that BUP, in any of his formulations, when compared with other antidepressants, has a greater safety profile compared to the appearance of sexual dysfunctions in its different manifestations. This places BUP as an appropriate alternative for sexually-active patients with MDD.

It has been demonstrated that sexual dysfunction is a frequent secondary effect of the SSRI and SNRI antidepressants in studies that show percentages between 40-70% of the patients treated with these drugs.[112-115] The incidence of sexual dysfunction secondary to antidepressant treatment is clearly underestimated by the clinicians while close to 40% of the patients treated consider it to be an unacceptable side effects, with elevated risk of treatment noncompliance. Because antidepressant treatment usually requires long term and even indefinite usage, the drug to be used should be effective and also assure a long-term level of tolerability that does not affect treatment compliance, helping the patient and the family to reach the best quality of life possible.[113]

In a meta-analysis performed by Thase, BUP showed a lower association with orgasmic dysfunction, a disorder of sexual arousal and sexual desire disorder, when compared with the SSRIs. With a risk of sexual dysfunction associated to treatment with BUP equal to that associated to placebo,[67] Clayton published the results of an observational study that recruited 6000 patients treated for depression with a wide variety of antidepressant drugs, emphasizing, among the results, that BUP was associated to a lower incidence of sexual dysfunction among all the drugs studied (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, mirtazapine and nefazodone). In patients without a condition associated to sexual dysfunction, risk of developing it was 4-6 times greater with the SSRIs or with Venlafaxine XR than that observed with BUP.[116]

The effect of BUP on sexual function has been compared with that of the SSRIs. Kennedy et al., in a multicenter, double-blind study to evaluate sexual function

Table 3 Adverse events related with the use of Bupropion, compared with SSRI and placebo

Adverse events	Bupropión N= 748 (%)	SSRIs - grouped N= 758 (%)	Placebo N= 524 (%)
Patients with side effects	81	83	77
Headaches	31	29	27
Dry mouth **	21	16	15
Nausea	17	21	14
Insomnia	17	16	7
Agitation	10	7	9
Diarrhea*	8	18	12
Somnolence*	3	12	5

*The events such as diarrhea and somnolence were significantly more frequent in the treatment with SSRI than in bupropion (p<0.001) ** Registry of dry mouth was more common in the treatment with bupropion than in those with SSRI (p=0.007)
Source: THASE ME, HAIGHT BR, RICHARD N, et al.: Depression remission rates following therapy with bupropion or selective serotonin reuptake inhibitors: a pooled analysis of original data from seven randomized controlled trials. J. Clin. Psychiatry (2005) 66:974-981

by gender (males versus females) in patients with MDD, randomized 141 patients to receive BUP-SR (150-300 mg/day) or paroxetine (20-40 mg/day), for 8 weeks. Measurement on the sexual function was made using the sexual effects scale (SexFX) and the scores obtained on the three subscales (desire, arousal and orgasm), in the treatment visits corresponding to weeks 2, 4, 6, and in the final treatment visit at 8 weeks. Lower scores were observed in women on the sexual function scales in the baseline visit versus men (mostly statistically significant). In the women treated with paroxetine, significantly lower scores were observed on all of the subscales and measurements in reference to BUP-SR (p<0.01). In men, and in the baseline visit, no significant differences were found in the scores of the SexFX (p=0.67). In the paroxetine treatment group, a decrease was observed in the scores on the SexFX during treatment (total SexFX p<0.002), desire (p<0.005), arousal (p<0.005) and global satisfaction (p<0.057). In the group under treatment with paroxetine, a significant deterioration was observed from the baseline visit to visit 8 in all the scores (p<0.01; arousal p<0.05). In the BUP-SR treated-males, no significant changes were observed in any of the measurements.[62]

Likewise, and in another specific analysis by gender, that compared BUP-SR and sertraline, it was demonstrated that the rate of male patients who experienced orgasmic dysfunction during the study was significantly greater for sertraline (61%) than for BUP (10%) (p<0.001), as also occurred in women (sertraline 41% *vs* BUP SR 7%; p<0.001).[61] Croft et al. showed in a comparative study with placebo group and between different drugs that the sexual dysfunction could be attributed to the treatment and not to the natural course of the disease. A smaller number of patients in the BUP SR treated group showed sexual desire disorders (19%) compared to sertraline (30%) (p<0.05) or placebo (31%). A higher number of patients with psychological sexual dysfunction in the sertraline-treated group was observed from day 14 versus the placebo (p<0.05). Only on day 56 were there more patients with BUP who has psychological sexual dysfunction versus the placebo group (p<0.05). The appearance of orgasmic dysfunction in sertraline-treated patients occurred after the seventh day of evaluation and remained significantly superior to placebo during the entire study (p<0.001). In relationship with orgasmic dysfunction, no statistically significant differences were found between BUP SR and placebo at any time of the study.[74] Coleman et al. observed the incidence of sexual function disorders with BUP and sertraline. At the end of the study, 13% of the BUP-treated patients, 17% of those in the placebo group and 39% of the sertraline treated patients had some sexual dysfunction. The incidence of sexual desire disorders was significantly higher with sertraline versus BUP (p<0.05). A total of 15% of the sertraline-treated patients after seven days of treatment already had orgasmic dysfunction compared with 5% in the case of the placebo group and 4% of the BUP SR-treated patients (p<0.05). In all of the treatment follow-up visits, the difference was significantly maintained in regards to the incidence of sexual functional disorders: 10% BUP, 14% placebo and 36% sertraline. At the eighth week, the percentage of patients treated with BUP SR who

Table 4 Adverse events observed during treatment with Venlafaxine XR or Bupropion XL

Side effect	Bupropión XL 300 – 450 mg/day N= 168 (%)	Venlafaxine XR 150 – 225 mg/day N= 174 (%)
Dry mouth	24	29
Nausea	15	26
Nasopharyngitis	10	5
Diarrhea	5	10
Decreased appetite	4	9
Somnolence	1	7
Sedation	1	6
Yawning	0	7

Source: Thase, M.E., et al., A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J.Clin.Psychopharmacol., 2006. 26(5): p. 482-488

improved their satisfaction in relationship with sexual function increased from 67% to 85%, in the placebo group from 69% to 81%, while it decreased in the sertraline from 70% to 62%.[72]

When fluoxetine was compared with BUP-SR, it was observed that the onset of orgasmic dysfunction occurred at week two of the study in a larger number of patients treated with fluoxetine then in those treated with BUP or placebo ($p<0.05$). The incidence of patients with orgasmic dysfunction who received the usual doses of fluoxetine was more than two times greater than that of those patients who received the usual doses of BUP SR (33% *vs* 15%); and was almost three times greater than that observed in the patients of the high dose BUP SR group (12%). It was not explained in the study if these differences were statistically significant. In all of the dose groups, the sexual dysfunction was greater in those patients treated with fluoxetine then in those treated with BUP SR. A greater proportion of patients under treatment with fluoxetine reported deterioration in their sexual function after the second week and during the entire treatment ($p<0.001$). No statistically significant differences were found between BUP and placebo.[73]

Clayton et al., in a randomized, double-blind clinical trial in two centers (data analyzed as study 1, study 2 and combined data), demonstrated that BUP XL/XR has the same impact as the SR formulation in the sexual sphere. This study compared BUP XL/XR, citalopram and placebo, demonstrating a similar antidepressant effect between both drugs ($p=0.533$), with emphasis on the presence of sexual dysfunction as a side effect of citalopram. In all the studies, the incidence of sexual dysfunction evaluated at the end of the treatment was significantly lower in the patients treated with BUP XL/XR compared to those treated with citalopram (study 1 and combined data: $p<0.001$; study 2: $p<0.05$). No significant differences were found regarding BUP XL/XR versus placebo (study 1: $p=0.348$ study 1; study 2: $p=0.094$ study 2 and combined data: $p=0.067$). The incidence of sexual dysfunction was higher with citalopram than with placebo for both studies and for the combined data ($p<0.001$). In both studies, and in the analysis of the combined data, the incidence of deterioration of the sexual function was significantly lower with BUP XL/XR than with citalopram (study 1: $p<0.001$; study 2 and combined data: $p<0.05$). No significant differences were found between BUP XL/XR and placebo in regards to their repercussion on sexual function (study 1: $p=0.279$; study 2: $p=0.389$ and combined data: $p=0.169$).[84]

Thase et al. found a significantly more favorable profile regarding sexual function for BUP XL/XR compared with venlafaxine. In males, there were statistically significant differences in favor of BUP XL/XR in all of the evaluations performed ($p\leq0.048$); while for women, the differences were significant in specific evaluations performed at weeks 5 and 6, and in the average of the evaluations of week 6 to 12 ($p\leq0.043$). The score on the sexual function scale with venlafaxine XR deteriorated after the second week ($p\leq0.002$), while in the case of BUP XL/XR, there were no changes compared to the onset ($p\geq0.285$). BUP XL/XR was statistically superior to venlafaxine in the pleasure, desire/frequency, desire/interest, psychological sexual dysfunction and orgasm evaluation subscales, in the evaluations performed at weeks 5, 6, 9 and 12 ($p\leq0.011$).[85]

Clinical efficacy in patients with SSRI induced sexual dysfunction

SSRI-induced sexual dysfunction is one of the most frequent causes of dropout from antidepressant treatment. The effect on sexual function presented by antidepressants which have an action mechanism of inhibition of serotonin reuptake (specific and also those associated with norepinephrine) has been thoroughly investigated. Montejo et al. described a mean incidence of sexual function disorders of 59.1% for all of the drugs studied (fluoxetine 57.7%; sertraline 62.9%; fluvoxamine 62.3%; paroxetine 70.7%; citalopram 72.7%; venlafaxine 67.3%; mirtazapine 24.4%; nefazodone 8%; *amineptine* 6.9%; moclobemide 3.9%). This same study observed a

higher incidence of sexual dysfunction in men (62.4%) than in women (56.9%).[113]

Several studies have been made to evaluate the role of BUP as an antidote of SSRI-induced sexual dysfunction.[117, 118] In patients under treatment with SSRI and with complaints of sexual dysfunction, Ashton observed that 52 out of the 75 complaints treated with low doses of BUP showed favorable results.[119] Clayton et al., in a double blind study in 42 patients previously treated with SSRI and who experienced general or specific sexual dysfunction, evaluated the effect of BUP SR versus placebo. It was observed that BUP SR, at a dose of 150 mg administered two times a day, was an effective rescue drug in relationship to sexual dysfunction as desire to initiate a sexual relation as well as their frequency increased. In the same way, a statistically significant increase was found in the level of baseline testosterone after treatment with BUP.[120]

Gardner et al. administered BUP between 300 and 600 mg/day for 4 to 26 months to 12 patient without any background of sexual dysfunction and to 28 with sexual dysfunction induced by tricyclic antidepressants, monoamine oxidase inhibitor, *maprotiline* or trazodone. The sexual dysfunction was resolved in 24 of the 28 patients when treatment was switched to BUP ($p<0.001$). The 12 patients without background of sexual dysfunction maintained conserved sexual function during the treatment with BUP.[121]

The possibility has been suggested of adding BUP to improve sexual dysfunction in depressed patients treated with other antidepressants. The data available suggests that, if it is well-tolerated, the combination of BUP and SSRI or SNRI can improve the antidepressive response.[122]

Agitation

Agitation may occur in patients with major depression, with a clinical manifestation that becomes apparent or is intensified during the use of antidepressant medication. Tollefson et al. analyzed that data of several clinical trials in 4737 patients with major depression assigned to receive SSRIs, tricyclic antidepressants or placebo. Most of the patients (>60%) had some grade of psychomotor agitation at the onset of the study and the rate of increase of the agitation during the acute phase of the treatment was not significantly different between the SSRIs, tricyclic antidepressants or placebo ($p>0.1$). Debut of agitation occurred with a non-significantly different incidence in the three treatment groups ($p>0.6$) and characteristically appeared during the first 3 weeks of treatment. It has not been determined if the incidence of agitation with BUP differs from other second generation antidepressants in the treatment of major depressive disorder.[107]

Nervousness

Sinclair et al.[123] identified four publications in a systematic review that responded to the question: *Which antidepressant drug is involved in the* jitteriness/anxiety *syndrome?).* In a randomized clinical trial of adverse events observed in panic attack disorder treatment, Yeragani et al.[124] demonstrated that imipramine caused significantly more cases of the jitteriness/anxiety syndrome versus placebo or diazepam. Among the limitations of this study are its reduced sample size (n=52) and the randomization and masking of the measurements are unknown. Beasley et al.[125] analyzed the data of a double blind clinical trial (n=706) of fluoxetine (up to 80 mg/day) *vs* imipramine (up to 300 mg/day) or placebo. The primary objective was to study the efficacy of fluoxetine in the treatment of depression and not the detection of the jitteriness/anxiety syndrome. However, the presence of agitation, anxiety, nervousness and insomnia was evaluated weekly and it was recorded if these symptoms were new or worsened in relationship to the baseline symptoms. more symptoms were observed in patients who received fluoxetine (28%) compared to placebo (17%). No significant difference was found between the number of symptoms in the patients who received imipramine compared to placebo. There was discontinuation of treatment due to the presence of symptoms with: fluoxetine (5%), imipramine (5%) and placebo (0%), a statistically significant difference for both medications compared to placebo. Harada et al.,[126] in a retrospective study of patients who received antidepressant medication, determined that paroxetine, fluvoxamine, milnacipran, amoxapine, clomipramine and mianserin were involved in the presentation of jitteriness/anxiety syndrome. Tollefson et al.[127] evaluated a North American database on the use of new antidepressant medication. The appearance of new symptoms or deterioration of them on the psychomotor agitation symptoms scale (Hamilton Rating Scale for Depression, HRSD) were considered to be intermediate variables to evaluate the appearance of the jitteriness/anxiety syndrome. No significant differences were found between the incidence of worsening of psychomotor symptoms (among them the jitteriness/anxiety syndrome) and the use of fluoxetine, tricyclic anti-depressants or placebo. The evidence regarding the incidence of jitteriness/anxiety syndrome among the antidepressant medications is not very strong. It has not been determined that the incidence of psychomotor agitation in patients treated for MDD with BUP differs from other second-generation antidepressants.[107]

Sleep disorders

In a study of Croft et al. (1999) in which 360 patients with MDD were randomized to receive BUP-SR, sertraline

or placebo, it was observed that significantly more patients treated with sertraline presented somnolence compared to those treated with BUP-SR (17% sertraline, 3% BUP-SR; p<0.05) [Croft, 1999 #56]. This same relationship was observed by Trivedi (2001) in a retrospective analysis of two studies having identical design that compared, among other parameters, the adverse effects of sertraline and BUP-SR on the central nervous system. No differences were observed between one group and another of treatment except for somnolence that occurred more frequently in the sertraline- treatment group compared to the group treated with BUP-SR (p<0.001).[75]

Convulsions

Due to its clinical importance, the principal adverse effect of treatment with antidepressants, and in this case, BUP, is the risk of seizures. The incidence of seizures in BUP-treated patients is related with the doses administered and with a previous history of seizures.[104] In a prospective, multicenter, open label study in 3100 patients with depression and no background of seizures, BUP SR was administered for 8 weeks in the acute phase of treatment and during the maintenance phase of up to one year. The maximum dose indicated was 300 mg/day (150 mg BID). During both phases, the incidence of seizures and other related adverse events were evaluated. During the acute phase, 2/3094 evaluable patients had seizures (0.06% - UL-95% CI 0.14%), and during the acute and continued maintenance phases, 3 seizures were observed in 3094 patients (0.10% UL-95% CI: 0.19%). The survival analysis showed a cumulative rate of seizures of 0.08% (UL- 95% CI: 0.18%) in the acute phase and of 0.15% (UL-95% CI: 0.30%) for both combined phases.[128] A previous study having a similar design, but with BUP-IR at maximum doses of 450 mg/day found an incidence of 0.40% for seizures in the acute phase of treatment and showed the cumulative risk in the acute phase to be 0.38%. Cumulative risk at 720 days in the study with BUP-IR (450 mg/day) was 0.48%.[129]

Although there are no studies that directly compare both formulations regarding the incidence of seizures, the similarities in the design of both studies suggest that the most recent formulations of BUP have a lower incidence and risk of presenting seizures, which, in every case, are comparable with those found in the literature for the rest of the antidepressants on the market.[129]

Seizures, typically generalized motor ones, have been described with an incidence of 1/1000 expositions to 300 mg/day,[128] and its incidence is dose-related. This incidence is similar to that which has been seen with other antidepressants, such as SSRIs.[130] It is important to study all of the patients in whom treatment is considered with BUP to detect predisposition to seizures. Thus, the maximum approved dose in Europe is 300 mg/day.

To minimize the risk of seizures, the patients should be questioned about predisposing factors, clinical or subclinical diseases and use of concomitant medications that may reduce the seizure threshold.

Weight

Several studies have demonstrated the relationship between the administration of BUP and mild weight loss. Jefferson et al. compared BUP XL/XR versus placebo and found a statistically significant difference in the patients' weight at the end of the study. The group of patients under treatment with BUP had a weight loss corresponding to 1.1 kg after 8 weeks of treatment while in the placebo group, there was a weight gain of 0.2 kg during the same time period (p<0.05).[83]

Body weight gain has been observed when dealing with antidepressants with serotoninergic or histamine effects.[131] BUP has no affinity for these receptors and does not cause weight gain, in any case, a mild decrease in weight. One 6-week long study on BUP IR versus nortriptyline showed a mean decrease of 0.82 kg in the BUP-treated patient group and a mean increase of 0.95 kg in those treated with nortriptyline compared to that at the initiation of the treatment (p<0.001).[70]

Croft et al. observed a slight weight loss in a study whose purpose was to determine the long-term incidence of BUP SR on body weight of the patients classified according to their Body Mass Index. However, this was not significant regarding the placebo at the end of the study (52 weeks).[132]

Cardiovascular events

Elderly patients with depression, with cardiovascular risk and cardiac backgrounds or conduction disorders are candidates to be treated with BUP before being treated with other antidepressant drugs because no alterations of the cardiac conduction have been observed during their use.[133]

Roose et al. evaluated the safety of BUP in 36 patients with cardiac disease (right ventricular failure, ventricular arrhythmia and conduction disorders). Although an increase was observed in blood pressure in the supine position, no alterations of cardiac conduction, orthostatic hypotension, arterial pulse affectation or exacerbation of ventricular arrhythmias after the

administration of BUP were observed.[133] Furthermore, and compared to tricyclic antidepressants such as **amitriptyline**, BUP did not cause alterations of the cardiac conduction, while amitriptyline was characterized by inducing a significant prolongation of the PR interval and of the QRS segment duration.[134] No changes induced by BUP were observed in the ECG (PR interval, QRS segment duration, QTc interval and QRS height) at therapeutic doses equivalent to those of amitriptyline. The results show that BUP does not seem to cause alterations in the cardiac conduction, a positive characteristics for patients with a background of cardiovascular disease or in patients with backgrounds of overdosage.[135] In patients hospitalized with MDD treated with tricyclic antidepressants and subsequent orthostatic hypotension, it has been demonstrated that BUP, after normalization for the placebo effect, does not provoke alterations in heart rate, systolic blood pressure or arterial hypertension compared to the placebo.[136] Kiev found similar findings in a subsequent study versus nortriptyline.[137]

Thase et al. observed that a greater number of patients under treatment with venlafaxine had clinically significant changes in systolic blood pressure (≥20 mmHg, BUP XL/XR 9%, venlafaxine XR 18%,) or in diastolic blood pressure (≥15 mmHg, BUP XL/XR 13%, venlafaxine XR 17%) compared to BUP. Furthermore, a greater number of patients under treatment with venlafaxine had sustained increases of systolic blood pressure (≥20 mmHg in 3 consecutive visits, BUP XL/XR 3%, venlafaxine XR 8%), and in diastolic blood pressure (≥15 mmHg in 3 consecutive visits, BUP XL7XR 6%, venlafaxine XR 11%). They did not observe clinically significant changes in pulse rate. There are no data on the statistical significance of these differences.[85]

However, Jefferson et al. reported the appearance of hypertension which, in some cases, can be severe and require acute treatment in patients who received BUP, both patients with pre-existing hypertension or not.[83] Blood pressure should be determined at the beginning of the study and the subsequent follow-up made, especially in patients with hypertension. If a clinically significant increase of blood pressure is observed, the possibility of interrupting treatment should be considered. Concomitant use of BUP and a Nicotine Transdermal System (NTS) can give rise to increases in blood pressure.[104]

Suicide

MDD is associated to an increase in risk of suicidal ideation, self-harm and suicides. This risk persists until remission of the disease and should be taken into account especially at the initiation of treatment and when changing doses. It is of general clinical experience that in all antidepressant therapies, the risk of suicide may increase in the early stages of recovery, although specific studies in soldiers discharged with a diagnosis of depression show that antidepressive treatment significantly decreases the risk of suicidal ideation and suicides in regards to those patients without treatment.[138]

It is recommended to provide special monitoring for patients with backgrounds of suicidal ideation or behavior. Because improvement of the clinical pictures generally takes approximately four weeks to appear, the patients should be controlled before and during the improvement period. The patients and their caregivers should receive instruction on this control and, above all, keep in mind the indication of coming to the consultation and/or getting into contact with their physician if they have suicidal thoughts, ideation or behavior.

Balit (2003) analyzed the effects of intentional and accidental overdose of BUP in 10 children and 59 adults. None of the patients followed-up by the center died and the side effects in children were minor, since only one patient had vomiting and hallucinations. Only 19% of the adults had taken BUP alone. The rest had taken it combined with other drugs. A total of 37% evolved with seizures, related with a mean dose that was much higher than those who did not have seizures (p=0.02). All the seizures were short and self-limiting. The rest of the symptoms corresponded to sinus tachycardia, hypertension, gastrointestinal symptoms and agitation.[139] Another study revealed that only 15% of the patients with elevated and intentional overdose had seizures and rarely had cardiovascular alterations. Most of the involuntary overdoses caused minimum alterations, while the presence of seizures is associated to intentionality and high doses.[140] Overdose of BUP has given rise to the appearance of symptoms that include somnolence, loss of consciousness and/or changes in the ECG such as alterations in conduction (including QRS prolongation), arrhythmias and tachycardia. Prolongation of the QTc interval has also been reported, generally observed together with QRS prolongation and an increase in heart rate. Most of the patients recover without sequels, and deaths related with bupropion in patients who take massive doses of the medication have rarely been reported.[103]

Synthesis of the safety of bupropion

For years, after the introduction of the tricyclic antidepressants (TADs) and MAOIs in the treatment of

depression, the fundamental was the efficacy of these drugs, while the side effects and other variants were relegated to a secondary factor.

However, in the last 20 years, above all since the introduction of Selective Serotonin Reuptake Inhibitors (SSRI), not only has efficacy been considered but also drugs safety and tolerability. The patients are no longer only evaluated regarding their recovery but also regarding other variables (sexual function, weight, etc.).

Along this line, BP not only has been demonstrated to be an excellent antidepressant but it also has good safety and tolerability. The results obtained in any of the age groups studied, from childhood to elderly, profile this drug as safe and effective.

The side effects of BUP compared to placebo, nortriptyline, venlafaxine or SSRI indicate that BUP has better tolerability and fewer side effects. Specifically, three studies indicate that the side effects of BUP are only superior to placebo in headaches, mouth dryness, nauseas, constipation, insomnia and allergic reactions.

On the other hand, it is interesting that the sexual dysfunctions with BUP are inferior to those occurring with SSRI, venlafaxine and antidepressants in general. Considering that the abandonments because of antidepressants are due to, above all, sexual dysfunctions and weight gain, it is very important that neither of these occur with BUP, which assures fewer abandonments.

Other side effects such as agitation, sleep disorders, seizures or cardiac alterations are not more frequent than with other antidepressants.

All of the above makes it possible to consider BUP as a safe and well-tolerated antidepressant that should be taken into consideration in the treatment of depression.

The value that the clinicians have given to the safety of antidepressant drugs in recent years has been growing progressively during that time. Therefore, increasingly greater importance is being given to the possible addictive capacity of the product, to the possible suicidality or to its influence on the psychophysiology and, due to the high prevalence of resistant depressions or depressions with partial response-remission, to its capacity to be combined with or to augment others.

BUP has been shown to be a drug that does not generate addictive behaviors or disorders in depressive patients or in patients with addictive disorders affected by depressive disorders, in spite of its dopaminergic-type molecular profile.

On the other hand, its efficacy and good tolerability in the treatment of detoxification of persons addicted to nicotine is very well known.

Because BUP has a respectful profile regarding sleep psychophysiology, eating behavior and especially sexual performance, have allowed BUP to be used in extended maintenance periods and for the prevention of relapses.

The third strength that BUP is currently considered to have is that related with its capacity to be combined with other antidepressants having a basically serotoninergic molecular profile.

Finally, its potent antidepressant capacity for persons with more severe and more inhibited depression should be acknowledged, avoiding suicidal risks.

In brief, it could be assumed that the safety profile of BUP not only facilitates monotherapy of persons diagnosed of depressive disorders but also its use in combination with other antidepressants in resistant depressions or in depressions with partial clinical remission-response. Thus, BUP can be considered an essential product to be considered in the decision making of the clinician.

CONCLUSIONS

BUP is an inhibitor of the reuptake of NE and DA without significant effects on the reuptake of 5-HT that has been available in different countries for more than 20 years. Even though its basic action mechanism is still unknown, some of the diagnostic symptoms of MDD have been associated to a decrease in dopaminergic activity and to reduced levels of NE and 5-HT. The use of BUP should be strictly supervised in patients with mild or moderate renal or hepatic failure and the risk-benefit of the administration of low doses in patients with severe renal failure should be evaluated. Its usage together with those drugs that inhibit enzyme complexes that participate in its metabolization or that are induced/inhibited by BUP should also be monitored. Even though the frequency in the appearance of seizures associated to the use of BUP is comparable to that found in the literature for the other antidepressants on the market, its use is not recommended in patients under treatment with drugs that can decrease the seizure threshold. As with all antidepressants, behaviors related with suicidal ideation or suicide attempts should be watched for, above all during the initiation of treatment, when there are changes of treatment or dose adjustment.

On the other hand, and considering the evidence collected in this article, the possible profiles of patients who could benefit from the clinical effect of BUP can be

Table 5 Comparison of side effects according to frequency of appearance (according to TF)

	Agitation	Jitteriness/ Restlessness/ Anxiety	Sleep disorders	Seizures	Sexual dysfunction	Others
Non-selective reuptake inhibitors of monoamines						
Amitriptyline	-	R (anxiety)	somnolence (not quantif.)	R	-	
Clomipramine	F	F	F	IF	VF	
Nortriptyline	-	IF (anxiety)	F	IF	IF	WEIGHT GAIN (F)
Trimipramine	+	-	+	+	-	
Selective serotonin reuptake inhibitors						
Citalopram	VF	VF (jitteriness) F (anxiety)	VF	IF	F	
Escitalopram	IF	IF (jitteriness) F (restlessness, anxiety)	IF	MR	F	WEIGHT GAIN (F)
Fluoxetine	+	+	+	+	+	
Fluvoxamine	F	F	F	R	IF	WEIGHT GAIN[141]
Paroxetine	VR	R (restlessness)	F	R	VF	WEIGHT GAIN (F)
Sertraline	F	F (anxiety)	VF	R	F	WEIGHT GAIN (IF)
Type A Monoamine Oxidase Inhibitors						
Moclobemide	IF	IF (anxiety)	F	-	-	
Other antidepressants						
Bupropion	F	F	VF	R	-	
Duloxetin	F	F	VF	R	F	
Mirtazapine	VR	R	F	R	-	WEIGHT GAIN (F)
Reboxetine	+	+	VF	-	F (men)	
Trazodone	NA	NA	NA	NA	NA	
Venlafaxine	IF	F (jitteriness)	F	R	F (men) IF (women)	WEIGHT GAIN (IF)

VF: Very frequent (≥1/10); F: Frequent (≥1/100, <1/10); IF: Infrequent (≥1/1,000, <1/100); R: Rare (≥1/10,000, <1/1,000); VR: Very rare (<1/1,0000); NA: Data sheet not available; +: described in Data sheet; HOWEVER, not quantifiable; -: The side effect is not reported in the data sheet

grouped according to these criteria: 1) clinical profile of the major depressive disorder presented by the patient, 2) profile of response to previous antidepressant treatments and 3) profile of aspects related with tolerability to ongoing antidepressants that are reported by the patient as determinants in their evaluation of the treatment. In regards to the first one, BUP should be considered as an antidepressant of choice in those patients who have the following relevant symptoms: loss of pleasure, of motivation and/or energy, hypersomnia, state of fatigue and/or alterations of the cognitive function. It has also been verified that the presence of an anxiety picture associated to major depression disorder should not affect the choice between BUP and SSRI, since the baseline levels of anxiety are not related with the antidepressant efficacy, nor are differences seen regarding them in the response to BUP or to the SSRI. In regards to the profile of response to previous antidepressive treatments, the efficacy of adding BUP for

the treatment of patients with inadequate response to previous treatments with tricyclic antidepressants and SSRI (those that provide a different action mechanism that entail the comprehensive approach to unbalanced potentials in the three monoamines related with the major depressive disorder: dopamine, norepinephrine and serotonine) and associated to dual antidepressants has been demonstrated. In regards to the aspects of tolerability reported in the medical office by the patient regarding the on-going antidepressant treatment, BUP should be considered of choice when these alterations include sexual dysfunction, somnolence or weight gain. Finally, in view of its good cardiovascular safety profile, lower incidence of somnolence observed during treatment with BUP, null association to sexual function disorders and antidepressant efficacy similar to that observed with SSRI, its use has been suggested in adult patients with conserved sexual function and in patients over 60 years or with comorbidities and/or cardiovascular backgrounds. In elderly patients, BUP has also been demonstrated to have a significant effect on the cognitive and social functioning level.

Among the adverse events most frequently associated to BUP, the following have been described: dry mouth (having a more frequent appearance than in treatment with SSRI) and insomnia, although the latter occurs with a similar frequency to that described with SSRI. However, in comparison with the frequency of appearance described in patients treated with BUP, adverse events such as diarrhea and somnolence appear more frequently associated to treatment with SSRI.

In regards to dosage, therapeutic doses between 150 mg and 300 mg have been demonstrated effective. Its administration in a single daily dose favors treatment adherence and therefore the likelihood of a remission of the depressive episode.

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CONFLICT OF INTERESTS

Dr. Carles Iglesies, co-author in this article, is the Scientific Director of the company Salutis Research, S.L.. Equally, Mr. Víctor Iriarte forms a part of the professional team of GlaxoSmithKline (GSK).

The remaining authors have not reported any type of conflict of interest.

REFERENCES

1. Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: a systematic review of the literature. Can J Psychiatry 2004;49:124-38.
2. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004;1:21-7.
3. Kruijshaar ME, Barendregt J, Vos T, de GR, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. Eur J Epidemiol 2005;20:103-11.
4. Zimmerman M, Posternak MA, Attiullah N, et al. Why isn't bupropion the most frequently prescribed antidepressant? J Clin Psychiatry 2005;66:603-10.
5. Lopez-Ibor JJ, Alonso J, Haro JM. Estudio Europeo de la Epidemiología de los Trastornos Mentales (ESEMeD): aportaciones para la salud mental en España. Actas Esp Psiquiatr 2007;35:1-3.
6. Instituto Nacional de Es. Anuario Estadístico de España - Salud. 2007;200-45.
7. American Psychiatric Association www.psych.org; http://www.psychiatryonline.com/resourceTOC.aspx?resourceID=1.
8. World Health Organization W. http://www.who.int/classifications/apps/icd/icd10online/.
9. Papakostas GI. Dopaminergic-based pharmacotherapies for depression. Eur Neuropsychopharmacol 2006;16:391-402.
10. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395-401.
11. Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. Expert Rev Neurother 2006;6:1249-65.
12. Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983;44:121-9.
13. Davidson J, Miller R, Van Wyck Fleet J, et al. A double-blind comparison of bupropion and amitriptyline in depressed inpatients. J Clin Psychiatry 1983;44:115-7.
14. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry* 1983;44:118-20.
15. Othmer E, Othmer SC, Stern WC, Van Wyck FJ. Long-term efficacy and safety of bupropion. JClinPsychiatry 1983;44:153-6.
16. Remick RA, Campos PE, Misri S, Miles JE, Van Wyck Fleet J. A comparison of the safety and efficacy of bupropion HCL and amitriptyline HCL in depressed outpatients. Prog Neuropsychopharmacol Biol Psychiatry 1982;6:523-7.
17. Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. J Clin Psychopharmacol 1986;6:27-32.
18. Branconnier RJ, Cole JO, Ghazvinian S, Spera KF, Oxenkrug GF, Bass JL. Clinical pharmacology of bupropion and imipramine in elderly depressives. J Clin Psychiatry 1983;44:130-3.

19. Clayton A. Extended-release bupropion: an antidepressant with a broad spectrum of activity? *8*: Expert Opinion Pharmacotherapy 2007;457-66.
20. Wilkes S. Bupropion. Drugs Today (Barc) 2006;42:671-81.
21. Soroko FE, Maxwell RA. The pharmacologic basis for therapeutic interest in bupropion. J Clin Psychiatry 1983;44:67-73.
22. Bryant SG, Guernsey BG, Ingrim NB. Review of bupropion. Clin Pharm 1983;2:525-37.
23. Bredeloux P, Dubuc I, Costentin J. Comparisons between bupropion and dexamphetamine in a range of in vivo tests exploring dopaminergic transmission. Br J Pharmacol 2007;150:711-9.
24. Argyelan M, Szabo Z, Kanyo B, et al. Dopamine transporter availability in medication free and in bupropion treated depression: a 99mTc-TRODAT-1 SPECT study. J Affect Disord 2005;89:115-23.
25. Learned-Coughlin SM, Bergstrom M, Savitcheva I, Ascher J, Schmith VD, Langstrom B. In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. Biol Psychiatry 2003:54:800-5.
26. Cooper BR, Wang CM, Cox RF, Norton R, Shea V, Ferris RM. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. Neuropsychopharmacology 1994;11:133-41.
27. Cooper BR, Hester TJ, Maxwell RA. Behavioral and biochemical effects of the antidepressant bupropion (Wellbutrin): evidence for selective blockade of dopamine uptake in vivo. J Pharmacol Exp Ther 1980;215:127-34.
28. Preskorn SH. Antidepressant response and plasma concentrations of bupropion. J Clin Psychiatry 1983;44:137-9.
29. Hamilton MJ, Smith PR, Peck AW. Effects of bupropion, nomifensine and dexamphetamine on performance, subjective feelings, autonomic variables and electroencephalogram in healthy volunteers. Br J Clin Pharmacol 1983;15:367-74.
30. Arias HR, Santamaria A, Ali SF. Pharmacological and neurotoxicological actions mediated by bupropion and diethylpropion. Int Rev Neurobiol 2009;88: 223-55.
31. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. Clin Ther 2005;27:1685-95.
32. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 2001;11:240-9.
33. Levesque M, Bedard A, Cossette M, Parent A. Novel aspects of the chemical anatomy of the striatum and its efferents projections. J Chem Neuroanat 2003;26:271-81.
34. D'Aquila PS, Collu M, Gessa GL, Serra G. The role of dopamine in the mechanism of action of antidepressant drugs. Eur J Pharmacol 2000;405:365-73.
35. Guiard BP, El Mansari M, Blier P. Prospect of a Dopamine Contribution in the Next Generation of Antidepressant Drugs: The Triple Reuptake Inhibitors. Curr Drug Targets, 2009.
36. Naranjo CA, Tremblay LK, Busto UE. The role of the brain reward system in depression. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:781-823.
37. Hamner MB, Diamond BI. Plasma dopamine and norepinephrine correlations with psychomotor retardation, anxiety, and depression in non-psychotic depressed patients: a pilot study. Psychiatry Res 1996;64:209-11.
38. Corcoran C, Wong ML, O'Keane V. Bupropion in the management of apathy. J Psychopharmacol 2004;18:133-5.
39. Kitamura Y, Yagi T, Kitagawa K, et al. Effects of bupropion on the forced swim test and release of dopamine in the nucleus accumbens in ACTH-treated rats. Naunyn Schmiedebergs Arch Pharmacol 2010;382:151-8.
40. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. Int J Neuropsychopharmacol 2005;8:93-105.
41. MacHale SM, Lawrie SM, Cavanagh JT, et al. Cerebral perfusion in chronic fatigue syndrome and depression. Br J Psychiatry 2000;176:550-6.
42. Pae C-U, Lim H-K, Han C, et al. Fatigue as a core symptom in major depressive disorder: overview and the role of bupropion. Expert Rev Neurotherapeuthics 2007;7:1251-63.
43. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. Depress Anxiety 2002;16:4-13.
44. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. Depress Anxiety 2000;12(Suppl 1):69-76.
45. El Mansari M, Guiard BP, Chernoloz O, Ghanbari R, Katz N, Blier P. Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. CNS Neurosci Ther 2010;16:e1-17.
46. Faucette SR, Hawke RL, Lecluyse EL, et al. Validation of bupropion hydroxylation as a selective marker of human cytochrome P450 2B6 catalytic activity. Drug Metab Dispos 2000;28:1222-30.
47. Faucette SR, Hawke RL, Shord SS, Lecluyse EL, Lindley CM. Evaluation of the contribution of cytochrome P450 3A4 to human liver microsomal bupropion hydroxylation. Drug Metab Dispos 2001;29:1123-9.
48. Bondarev ML, Bondareva TS, Young R, Glennon RA. Behavioral and biochemical investigations of bupropion metabolites. Eur J Pharmacol 2003;474:85-93.
49. Daviss WB, Perel JM, Birmaher B, et al. Steady-state clinical pharmacokinetics of bupropion extended-release in youths. J Am Acad Child Adolesc Psychiatry 2006;45:1503-9.
50. Cooper TB, Suckow RF, Glassman A. Determination of bupropion and its major basic metabolites in plasma by liquid chromatography with dual-wavelength ultraviolet detection. J Pharm Sci 1984;73:1104-7.
51. Findlay JW, Van Wyck FJ, Smith PG, et al. Pharmacokinetics of bupropion, a novel antidepressant agent, following oral administration to healthy subjects. Eur J Clin Pharmacol 1981;21:127-35.
52. Baab SW, Peindl KS, Piontek CM, Wisner KL. Serum bupropion levels in 2 breastfeeding mother-infant pairs. J Clin Psychiatry 2002;63:910-1.
53. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. Ann Pharmacother 1993;27:431-3.
54. Fava M, Rush AJ, Thase ME, *et al.* 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. Prim Care Companion J Clin Psychiatry 2005;7:106-13.
55. Hesse LM, Venkatakrishnan K, Court MH, et al. CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants. Drug Metab Dispos 2000;28:1176-83.
56. Guzey C, Norstrom A, Spigset O. Change from the CYP2D6 extensive metabolizer to the poor metabolizer phenotype during treatment With bupropion. Ther Drug Monit

2002;24:436-7.
57. Hamilton MJ, Bush MS, Peck AW. The effect of bupropion, a new antidepressant drug, and alcohol and their interaction in man. Eur J Clin Pharmacol 1984;27:75-80.
58. Peck AW, Stern WC, Watkinson C. Incidence of seizures during treatment with tricyclic antidepressant drugs and bupropion. J Clin Psychiatry 1983;44:197-201.
59. Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. J Clin Psychiatry 1990;51:194-9.
60. Reimherr FW, Cunningham LA, Batey SR, Johnston JA, Ascher JA. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. Clin Ther 1998;20:505-16.
61. Kavoussi RJ, Segraves RT, Hughes AR, Ascher JA, Johnston JA. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58:532-7.
62. Kennedy SH, Fulton KA, Bagby RM, Greene AL, Cohen NL, Rafi-Tari S. Sexual function during bupropion or paroxetine treatment of major depressive disorder. Can J Psychiatry 2006;51:234-42.
63. Weihs KL, Settle EC, Jr., Batey SR, Houser TL, Donahue RM, Ascher JA. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61:196-202.
64. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biol Psychiatry 2002;51:753-61.
65. Goodnick PJ, Dominguez RA, DeVane CL, Bowden CL. Bupropion slow-release response in depression: diagnosis and biochemistry. Biol Psychiatry 1998;44:629-32.
66. Doraiswamy PM, Khan ZM, Donahue RM, Richard NE. Quality of life in geriatric depression: a comparison of remitters, partial responders, and nonresponders. Am J Geriatr Psychiatry 2001;9:423-8.
67. Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry 2005;66:974-81.
68. Fabre LF, Brodie HK, Garver D, Zung WW. A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. J Clin Psychiatry 1983;44:88-94.
69. Zung WW, Brodie HK, Fabre L, McLendon D, Garver D. Comparative efficacy and safety of bupropion and placebo in the treatment of depression. Psychopharmacology (Berl) 1983;79:343-7.
70. Masco HL, Kiev A, Holloman LC, Johnston JA, Lineberry CG. Safety and efficacy of bupropion and nortriptyline in outpatients with depression. Current Therapeutic Research 1994;55:851-63.
71. Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991;52:329-35.
72. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999;11:205-15.
73. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 2001;23:1040-58.
74. Croft H, Settle E, Jr., Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;21:643-58.
75. Trivedi MH, Rush AJ, Carmody TJ, et al. Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? J Clin Psychiatry 2001;62:776-81.
76. Papakostas GI, Montgomery SA, Thase ME, Katz JR, Krishen A, Tucker VL. Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. J Clin Psychiatry 2007;68:1907-12.
77. Fava M, Papakostas GI, Petersen T, et al. Switching to bupropion in fluoxetine-resistant major depressive disorder. Ann Clin Psychiatry 2003;15:17-22.
78. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354:1231-42.
79. Granger AL, Fehnel SE, Hogue SL, Bennett L, Edin HM. An assessment of patient preference and adherence to treatment with Wellbutrin SR: a web-based survey. J Affect Disord 2006;90:217-21.
80. Hewett K, Chrzanowski W, Schmitz M, et al. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. J Psychopharmacol 2008.
81. Thase ME, Clayton AH, Chrzanowski W, et al. Bupropion extended release and venlafaxine extended release for the treatment of depression: results from three multicenter trials. Eur Psychiatry 2006; 21:S168.
82. Hewett K, Chrzanowski W, Jokinen R, et al. Double-blind, placebo-controlled evaluation of extended-release bupropion in elderly patients with major depressive disorder. J Psychopharmacol 2009.
83. Jefferson JW, Rush AJ, Nelson JC, et al. Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2006;67:865-73.
84. Clayton AH, Croft HA, Horrigan JP, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry 2006;67:736-46.
85. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol 2006;26:482-8.
86. Ferguson J, Cunningham L, Merideth C, et al. Bupropion in tricyclic antidepressant nonresponders with unipolar major depressive disorder. Ann Clin Psychiatry 1994;6:153-60.
87. Apter JT, Kushner SF, Woolfolk RL. Bupropion/nortriptyline combination for refractory depression. Ann Clin Psychiatry 1994;6:255-8.
88. DeBattista C, Solvason HB, Poirier J, Kendrick E, Schatzberg AF. A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. J Clin Psychopharmacol 2003;23:27-30.

89. Spier SA. Use of bupropion with SRIs and venlafaxine. Depress Anxiety 1998;7:73-5.
90. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
91. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry 2008;65:870-80.
92. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354:1243-52.
93. Bodkin JA, Lasser RA, Wines JD, Jr., Gardner DM, Baldessarini RJ. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58:137-45.
94. Papakostas GI, Worthington JJ, III, Iosifescu DV, et al. The combination of duloxetine and bupropion for treatment-resistant major depressive disorder. Depress Anxiety 2006;23:178-81.
95. Herrera-Guzman I, Gudayol-Ferre E, Lira-Mandujano J, et al. Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. Psychiatry Res 2008;160:72-82.
96. Gualtieri CT, Johnson LG. Bupropion normalizes cognitive performance in patients with depression. Med Gen Med 2007;9:22.
97. Verbeeck W, Tuinier S, Bekkering GE. Antidepressants in the treatment of adult attention-deficit hyperactivity disorder: a systematic review. Adv Ther 2009;26:170-84.
98. Rush AJ, Trivedi MH, Carmody TJ, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. Neuropsychopharmacology 2001;25:131-8.
99. Papakostas GI, Trivedi MH, Alpert JE, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of anxiety symptoms in major depressive disorder: a meta-analysis of individual patient data from 10 double-blind, randomized clinical trials. J Psychiatr Res 2008;42:134-40.
100. Bryant SG, Brown CS. Current concepts in clinical therapeutics: major affective disorders, Part 1. Clin Pharm 1986;5:304-18.
101. Fortner MR, Brown K, Varia IM, Gersing KR, O'Connor C, Doraiswamy PM. Effect of Bupropion SR on the Quality of Life of Elderly Depressed Patients With Comorbid Medical Disorders. Prim Care Companion J Clin Psychiatry 1999;1:174-9.
102. Rousseaus R WDHK. Efficacy and safety of bupropion XL in elderly patients with major depressive disorder. Poster presentation at the 19th American Psychiatric Association Annual Meeting.
103. DeVane CL, Laizure SC, Stewart JT, et al. Disposition of bupropion in healthy volunteers and subjects with alcoholic liver disease. J Clin Psychopharmacol 1990;10:328-32.
104. AGEMED. Ficha Técnica del Producto: Elontrin. In: Social AEdMyPS-MdSyP, ed. *https://sinaem4agemedes/consaem/especialidaddo?metodo=verFichaWordPdf&codigo=68615&formato=pdf&formulario=FICHAS*, 2009.
105. Chun-Fai-Chan B, Koren G, Fayez I, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obstet Gynecol 2005;192:932-6.
106. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. PharmacoepidemiolDrug Saf 2007;16:474-84.
107. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2008;149:725-33.
108. Settle EC, Stahl SM, Batey SR, Johnston JA, Ascher JA. Safety profile of sustained-release bupropion in depression: results of three clinical trials. Clin Ther 1999;21:454-63.
109. Wellbutrin (bupropion) tablets, Wellbutrin SR (bupropion) and Wellbutrin XL (bupropion). Physician's Desk Reference Thomson PDR, Montvale, NJ. 2005: 1655-1668.
110. Modell JG, Rosenthal NE, Harriett AE, et al. Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. Biol Psychiatry 2005;58:658-67.
111. Weisler RH, Johnston JA, Lineberry CG, Samara B, Branconnier RJ, Billow AA. Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol 1994;14:170-9.
112. Montejo AL, Rico-Villademoros F. Psychometric properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. J Sex Marital Ther 2008;34:227-39.
113. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry 2001;62(Suppl 3):10-21.
114. Fava M, Rankin M. Sexual functioning and SSRIs. J Clin Psychiatry 2002;63(Suppl 5):13-6; discussion 23-15.
115. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry 2006;67(Suppl 6):33-7.
116. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63:357-66.
117. Gitlin MJ, Suri R, Altshuler L, Zuckerbrow-Miller J, Fairbanks L. Bupropion-sustained release as a treatment for SSRI-induced sexual side effects. J Sex Marital Ther 2002;28:131-8.
118. Ginzburg R, Wong Y, Fader JS. Effect of bupropion on sexual dysfunction. Ann Pharmacother 2005;39:2096-9.
119. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry 1998;59:112-5.
120. Clayton AH, Warnock JK, Kornstein SG, Pinkerton R, Sheldon-Keller A, McGarvey EL. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry 2004;65:62-7.
121. Gardner EA, Johnston JA. Bupropion-an antidepressant without sexual pathophysiological action. J Clin Psychopharmacol 1985;5:24-9.
122. Zisook S, Rush AJ, Haight BR, Clines DC, Rockett CB. Use of bupropion in combination with serotonin reuptake inhibitors. Biol Psychiatry 2006;59:203-10.
123. Sinclair LI, Christmas DM, Hood SD, et al. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry 2009;194:483-90.
124. Yeragani VK, Pohl R, Balon R, Ramesh C, Weinberg P. Imipramine-induced jitteriness and decreased serum iron levels. Neuropsychobiology 1992;25:8-10.
125. Beasley CM, Jr., Sayler ME, Bosomworth JC, Wernicke JF. High-

dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. J Clin Psychopharmacol 1991;11:166-74.
126. Harada T. A survey of activation syndrome induced by antidepressants. Int Clin Psychopharmacol 2006;21:A9.
127. Tollefson GD, Sayler ME. Course of psychomotor agitation during pharmacotherapy of depression: analysis from double-blind controlled trials with fluoxetine. Depress Anxiety 1996;4:294-311.
128. Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998;59:366-73.
129. Johnston JA, Lineberry CG, Ascher JA, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry 1991;52:450-6.
130. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. Int J Clin Prac*t* 2005;59:1435-40.
131. Masand PS, Gupta S. Long-term side effects of newer-generation antidepressants: SSRIS, venlafaxine, nefazodone, bupropion, and mirtazapine. Ann Clin Psychiatry 2002;14:175-82.
132. Croft H, Houser TL, Jamerson BD, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. Clin Ther 2002;24:662-72.
133. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. Am J Psychiatry 1991;148:512-6.
134. Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. J Clin Psychiatry 1983;44:174-5.
135. Isbister GK, Balit CR. Bupropion overdose: QTc prolongation and its clinical significance. Ann Pharmacothe*r* 2003;37:999-1002.
136. Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. J Clin Psychiatry 1983;44:170-3.
137. Kiev A, Masco HL, Wenger TL, Johnston JA, Batey SR, Holloman LC. The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. Ann Clin Psychiatry 1994;6:107-15.
138. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry 2007;164:1044-9.
139. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. Med J Aust 2003;178:61-3.
140. Belson MG, Kelley TR. Bupropion exposures: clinical manifestations and medical outcome. J Emerg Med 2002;23:223-30.
141. Tutka P, Mroz T, Klucha K, Piekarczyk M, Wielosz M. Bupropion-induced convulsions: preclinical evaluation of antiepileptic drugs. Epilepsy Res 2005;64:13-22.
142. Foote S, Aston-Jones G. Pharmacology and physiology of central noradrenergic systems. In: Bloom F, Kupfer DJ e, eds. Psychopharmacology: the fourth generation of progress. New York: Raven Press Ltd, 1995; p. 335-45.
143. Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. J Clin Psychiatry 2008;69(Suppl E1):4-7.
144. Papakostas G, Cooper J, Richard N. Resolution of sleepiness and fatigue: a comparison of bupropion and SSRIs in patients achieving remission in MDD. European Psychiatry 2008;23:abstract P0046.
145. Shelton RC, Tomarken AJ. Can recovery from depression be achieved? Psychiatr Serv 2001;52:1469-78.
146. Stahl S, ed. Essential Psychopharmacology. Second edition edn. New York, NY: Cambridge University Press, 2000.
147. Stahl SM. Deconstructing psychiatric disorders, part 2: An emerging, neurobiologically based therapeutic strategy for the modern psychopharmacologist. J Clin Psychiatry 2003;64:1145-6.