

Gemma García-Parés¹
 Josefina Pérez-Blanco²
 Manel Sánchez-Pérez³
 Carlos Roncero^{4, 5}
 Facund Forá⁶
 Verónica Galvez Ortiz⁷
 Narcís Cardoner-Álvarez⁷
 Jose M. Crespo-Blanco⁷
 Víctor Navarro-Odrizola⁸
 Grupo EUCB

Role of bupropion in the treatment of resistant depression. Management of bupropion in combination therapy

¹Programa Clínico Depresión
 Servicio de Psiquiatría

²Instituto Clínico de Neurociencias
 Hospital Clínic de Barcelona

³Unitat de Psiquiatria Geriàtrica
 Sagrat Cor, Serveis de Salut Mental
 Martorell, Barcelona

⁴Servicio de Psiquiatría-CAS Vall d'Hebron
 Hospital Universitario Vall d'Hebron
 Agencia de Salud Pública de Barcelona (ASPB)

⁵Departamento de Psiquiatría
 Universidad Autónoma de Barcelona

⁶Psiquiatra
 Centro Médico Teknon

⁷Servicio de Psiquiatría
 Hospital Universitari de Bellvitge-IDIBELL
 CIBERSAM

⁸Programa Clínico Depresión
 Servicio de Psiquiatría
 Instituto Clínico de Neurociencias
 Hospital Clínic de Barcelona

One of the treatment strategies for the treatment of resistant depression consists in combining antidepressant drugs. Their combination with bupropion offers advantages over other possible combinations. The literature on this aspect and other possible indications for combination has been reviewed.

DEPRESSION RESISTANT

Introduction

The concept of resistant depression (RD) was born at the end of the 1960's once the efficacy trials for imipramine and derived tricyclics were completed. Since then, difference definitions have been drawn up, some of which are vague - that is, insufficient response to an adequate antidepressive treatment, and other more operational ones - that is, no response to two adequate trials with antidepressants belonging to different family. The non-response can be specified as "primary depression that does not respond to 300 mg of imipramine or equivalent antidepressants, nor to monoamine oxidase inhibitor (MAOI), with a minimum time to response of 6 week and always based on assuring treatment compliance."

Thase and Rush suggest staging resistance on five levels. A first level would be failure of response of at least one adequate trial with selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRI). A second level would be the first level plus failure of response to an antidepressant of different class, level 3 would be level 2 plus failure of response to a tricyclic antidepressant (TCA), level 4 would be level 3 plus failure of responses to monoaminoxidase inhibitors (MAOI) and finally level 5 would be level 4 plus failure of response to electroconvulsive therapy (ECT). This definition of Thase, however, has the disadvantage that it does not distinguish between partial and complete response and does not consider the possibilities of augmentation and combination strategies.¹⁻³

The importance of knowing what resistant depression (RD) is and what should be done is supported by the fact that 30-40% of the patients do not respond to the first treatment and 5-10% do not respond to more aggressive therapeutic strategies.

When a patient has resistant depression, the first step consists in verifying that we have not made the wrong diagnoses and that no other external causes are influencing the fact that it is resistant (comorbidity, drugs). We should also not forget to verify that both dose as well as treatment duration are adequate and whenever possible determine plasma levels of the drug, since these may be lower than expected (e.g. rapid metabolizer, enzymatic induction) or even nonexistent (we bring to mind that the percentage of patients who are non-complier's with the treatment is significant).

Once this is verified, there are four types of action strategies, and the choice of one or another will depend on several factors, such as whether there has or has not been a response to the first strategy or what is the predominant symptom in the clinical picture.

** Francisca Almansa, Carmen Barral, Milagrosa Blanca, Nagore Benito, Joan Cadevall, Horacio Casté, Nuria Custal, Anna Falcés, Eva Fontova, Juan Manuel Goicolea, Georgina González, Paul Ernesto González, Ana Herrero, Rafael Martín, Leticia Medeiros, Javier Merino, Laura Mora, Josep M^o Otín, Adolfo Pellejera, Rosa Pi, Cristina Pinet, Dolores Robles, Alejandro Rodríguez, Ferran Romaguera, Carme Romero, Carme Sarri, Joan Seguí, Sara Solé, Carmen Sotelo, Josep Tort, Marc Valenti.*

Correspondence:
 Narcís Cardoner Álvarez
 Servicio de Psiquiatría
 Hospital Universitari de Bellvitge-IDIBELL, CIBERSAM
 Feixa Llarga s/n
 08907
 Correo electrónico: ncardoner@bellvitgehospital.cat

Table 1

DEMONSTRATED SCIENTIFIC EVIDENCE	
Lithium salts	Add dose with which we obtain lithemia \approx 0.3-0.4 mmol/L (try $\frac{1}{2}$ -0- $\frac{1}{2}$ or $\frac{1}{2}$ - $\frac{1}{2}$ - $\frac{1}{2}$), and wait 3-4 weeks before deciding if it has not been effective. If it works, maintain it the same time as the antidepressant.
Triyodotironina (T3)	Add 25-50 μ g/d, a maximum of 8-12 weeks (if more, risk of hypothyroidism on withdrawal).
Atypical antipsychotics	Olanzapine, quetiapine, risperidone, at low doses.
SUGGESTIVE SCIENTIFIC EVIDENCE	
Buspirone	Partial antagonist of the presynaptic 5HT1A receptor. Use dose between 10-50 mg/day.
Pindolol	Antagonist of the presynaptic 5HT1A receptor. Dose: 2.5 mg 1-1-1. It is useful to decrease the latency time of the antidepressants.
Psychostimulants	Methylphenidate (5-40 mg/day), dextro-amphetamine (5-20 mg/day), modafinil (200-400 mg/day)
Dopaminergic agents	Pergolide (0.25-2 mg/day), amantadine (200-400 mg/day), pramipexole (0.375-1 mg/day) and bromocriptine (5 mg/day). It is believed that they can improve SSRI-induced sexual dysfunction.
Serotonin precursors	Tryptophan and 5-hydroxytryptophan. Little evidence and poor gastric tolerance.
Anti-seizures	Valproate, carbamazepine, lamotrigine, gabapentin.
Hormone treatments	Transdermal gel of testosterone: ♂ of 30 to 65 years with low levels of testosterone glucocorticoid antagonist: MDE + hypercortisolism or resistance to DXM suppression test)

MDE: major depressive episode. DXM: dexamethasone.

Optimization

This consists in forcing the dose up to the maximum recommended or tolerated for the patient and in prolonging the treatment duration without modifications up to 8 -10 weeks.

Augmentation

This means adding substances, without antidepressant neck cavity (or limited activity) that may increase the potency of the antidepressants. See summary in table 1.

Combination

The aim is to combine antidepressants with complementary action mechanisms: for example, combination of selective serotonin reuptake inhibitors (SSRIs) with selective norepinephrine reuptake inhibitors (SNRI) or combination of bupropion with a serotonin and norepinephrine reuptake inhibitor.

In spite of the many combinations that are being recommended, few have undergone a controlled study. One of the first combination strategies was that of the tricyclic antidepressants or MAOIs, but there is only one controlled study with this combination and the results were not superior to each treatment individually. This, and the risk of the combination, makes it of little use, although we should not forget it in the case of high resistance.^{4,5}

Substitution

It consists in substituting one antidepressant with another. A good description of this strategy is found in the articles of Alvarez and Janicak.^{6,7} They recommend switching to another antidepressant having a different class and action mechanism when one or two of the same family have not been effective.

ROLE OF BUPROPION IN THE TREATMENT OF RESISTANT DEPRESSION

Studies with therapeutic doses of up to 300 mg/day

At the end of the 1990s, several authors⁸⁻¹⁵ described the first positive results of the use of bupropion in resistant depressions. They are cases or retrospective reviews in which positive results were seen when bupropion was added to SSRI (sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram and paroxetine), to SNRI, specifically venlafaxine, or when switching from TCA or SSRI to bupropion, due to intolerance or poor response.

A recent study by Blier et al.,¹⁶ comparing the efficacy of an antidepressant alone, that is, fluoxetine, or a combination strategy from the beginning, fluoxetine with mirtazapine, mirtazapine with venlafaxine, or mirtazapine

Table 2 Augmentation with bupropion to improve the antidepressive effect

Study design	Dose regime	Results/Comments
Open studies		
Open -DeBattista-(19) Prospective of 6 weeks (N = 28) Inadequate response (≥ 15 in HDRS-24) to fluoxetine, paroxetine, sertraline, or venlafaxine	Bupropion 150 300 mg/day (mean dose = 270 mg/day) Mean daily doses: Fluoxetine = 40 mg Paroxetine = 34 mg Sertraline = 113 mg Venlafaxine = 75 mg	54% responded to the augmentation with bupropion SR, decrease of the HDRS and BDI scores from baseline values ($P < 0.001$) 64% had scores of 2 ("much improvement") or 1 ("much more improvement") in week 6 in the CGI evaluated by the clinician; 57% had similar scores in the CGI evaluated by the patients The most common AEs were headache, insomnia
Open -Ramasubbu R(14) Case series (N = 6) MDD or MDD plus dysthymia Partial remission with augmentation of lithium with fluoxetine, paroxetine or sertraline	1.Bupropion SR (150-300 mg/day) 2.Desipramine (75 150 mg/day)	3/5 patients with bupropion SR reached almost complete remission; 1 patients reached partial remission; 1 patient reached complete remission; 2 patients who began with desipramine switched to bupropion SR due to AEs
Open and Prospective Maron E21 Augmentation phase of 6 weeks N = 135 (n = 41 received augmentation) Inadequate response (≥ 15 in HDRS-24) to fluoxetine, paroxetine, sertraline or venlafaxine	Bupropion SR was initiated with 150 mg/day and increased up to 150 mg twice a day after week 2 or later if the response was insufficient Escitalopram 10-20 mg/day	After 6 weeks of augmentation, 61% of the patients were defined as responders and 53.7% reached remission 31.7% showed partial or insufficient response and 7.3 interrupted treatment due to adverse effects or lack of efficacy
AE= adverse events; BDI = Beck Depression Inventory; CGI = Clinical Global Impression Scale; HA = headache; HDRS-24 = Hamilton Depression Rating Scale; MDD = major depressive disorder; OCD=obsessive compulsive disorder; SIGH SAD = Structured Interview Guide for Hamilton Depression Rating Scale; SSRI = selective serotonin reuptake inhibitor		

with bupropion in patients with Major Depressive Disorder (MDD) showed a greater of response in the group treated with combinations. The percentage of remissions was 25% for fluoxetine in monotherapy, 52% for the combination of mirtazapine and fluoxetine, 58% for the combination of mirtazapine and venlafaxine and 46% for mirtazapine plus bupropion.

Table 2 summarizes other open prospective studies that have investigated the combination of bupropion (up to 300 mg/day) with other antidepressants to increase the antidepressive effect in patients who do not respond or partially respond to monotherapy

Studies with therapeutic doses superior to 300 mg/day

The Spier study¹⁷ reviewed a group of 25 patients with partial response or side effects, with SSRI or venlafaxine. Twelve of the 15 patients with partial response to monotherapy improved after adding bupropion (dose up to

450 mg/day). Ten more patients were treated with bupropion due to poor tolerability to serotonergic treatment and the adverse effects improved in 2 of the 10.

In a retrospective study, Bodkin¹⁶ described that 70% of a group of 27 patients with partial response to fluoxetine improved after adding bupropion (mean dose of 243 mg/day) and that the combination was well tolerated. However, it could not be concluded that the combination was better than each one the drugs individually. Dewan¹⁸ describes the case of a female patient resistant to paroxetine, who had gained 20 kilograms of weight and improved after adding bupropion (150 to 400 mg/day) to 30 mg of paroxetine, with the added advantage of losing 10 kilograms of weight.

In another open prospective study, Leuchter et al. found remission rates and responses that were superior to the escitalopram-bupropion combination (dose of bupropion of up to 400 mg/day) than with the known rates in the studies with SSRI in monotherapy.²² Of the 51 patients with recurrent or chronic MDD, the response rate was 62% and the remission rate 50%. The authors also stress the good tolerability and safety of the combination.

There are some efficacy data of bupropion in combination with duloxetine in resistant depression.²³

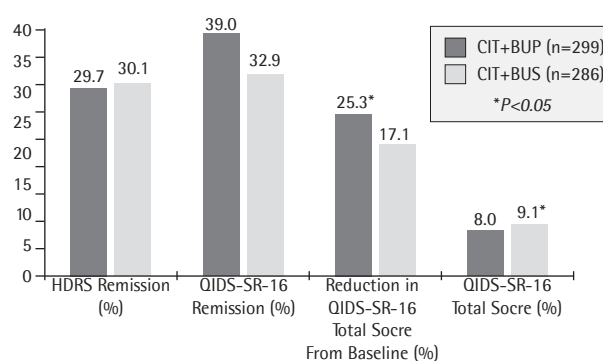
The data from the STAR-D (Sequenced Treatment Alternatives to Relieve Depression) study also provides us with information on bupropion in the treatment of resistant depression.^{2, 3, 24} The STAR-D study was designed as a several stage, multicenter, prospective and randomized clinical trial with depressed patients (non-psychotic major depression) in which several treatment options were compared for the patients who did not have a satisfactory response to citalopram. The study was designed to include samples that were generalizable and was conducted in 40 primary care and mental health centers. The patients included in the study were aged 18-75 years, had scores on the HDRS-17 scale of ≥ 14 , and who met the criteria of simple or non-psychotic recurrent major depression, according to the DSM-IV. As exclusion criteria, having: history of bipolar disorder, schizophrenia, schizoaffective disorder or psychosis; a background of intolerability or lack of effect to at least one protocol-based treatment in an adequate study; lack of response to an SRI in a recurrent episode of major depression in an adequate study; general medical conditions or concomitant therapy that would contraindicate any level (1 or 2) of treatment; or the need for treatment with antipsychotics or mood stabilizers.

Initially, the patients were treated on level 1 with citalopram. Those who did not achieve remission reached level 2 that included the combination with bupropion, sertraline or venlafaxine. The following levels included strategies of additional treatment. Inclusion in level 2 was due to a lack of remission or intolerability during the treatment with citalopram and acceptance of the treatment options. The patients were distributed according to their accepted treatment options and then randomized among the options they accepted.

Patients and medical professionals were not blinded to the treatment assigned or to the dose. The efficacy variables were: remission defined as having a score of ≤ 7 on the 17 item Hamilton scale (HDRS-17), final response as having $\geq 50\%$ reduction on the Quick Inventory of Depressive Symptomatology (QIDS-SR-16) scale and final remission as having QIDS-SR-16 ≥ 5 .

For potentiation, the dose of citalopram was maintained constant (it being possible to reduce it if adverse effects occurred). Besides citalopram, the patients received bupropion 200 mg/day x 2 weeks, increasing to 300 mg/day at the 4th weeks and to 400 mg/day during the 6th weeks, or buspirone 15 mg/day x 1 week, increased to 30 mg/day during week 2 and to 45 mg/day during weeks 3-5, with a maximum dose of 60 mg/day during week 6.

A total of 4,041 patients were included in level I, 1,439 reached level to 2. Of these, 565 were randomly assigned to



CIT: Citalopram, BUP: Bupropion, BUS: Buspirone

Figure 1

Level 2 of treatment: addition of buspirone or bupropion. Efficacy results

add citalopram, bupropion (n = 299, mean dose = 268 mg/day) or buspirone (n = 286, mean dose = 41 mg/day). There were no statistically significant differences between the two groups in regards to the primary variable, clinical remission, measured with HDRS. A total of 30% of each group achieved clinical remission. However, it should be stressed that the citalopram combined with bupropion reduced the QIDS-SR significantly more from the baseline level and was better tolerated than the combination with buspirone (figure 1).

Other indications of the combination

In spite of the limited evidence available for most of the combination strategies, based on the information collected in meetings with expert clinical psychiatrists, we know that these are frequently used in the specialized clinical practice. In the following, some of the combinations of bupropion with others psychopharmaceuticals are described, excluding their combined use in resistant depression.

Combination to reduce adverse effects

No studies that illustrate the combined use of bupropion with other antidepressants having a different purpose than that of potentiation have been found in the literature. However, due to its action profile and that of tolerability, the addition of bupropion to another antidepressant would make it possible to reduce the dose of the second drug and would have advantages in relationship to the decrease of adverse effects. Regarding the SSRI, bupropion has a better profile in the conservation of sexual function,²⁶ appetite stability and less somnolence.²⁷ The literature suggests that the substitution of an SSRI with bupropion could improve sexual dysfunction.^{28, 29}

Combination in Bipolar Depression

Although the studies on the convenience of using antidepressants in the treatment of Bipolar Depression are controversial, it has been suggested that bupropion combined with a mood stabilizer would be the best option. According to several authors, bupropion has less potential to induce the switch to hypomania or mania than desipramine or venlafaxine, probably due to its lower effects on the noradrenergic system. In the Leverich study, in the case of rapid cycling patients, bupropion induced a shift in a lower proportion than sertraline.^{30, 31}

We remind you that bupropion is principally metabolized through Cytochrome P450 isoenzyme 2B6. Both bupropion and its metabolite are potent inhibitors of CYP2D6 and their effect is maintained at least one week. Therefore, possible interactions with drugs that are preferentially metabolized by CYP2D6 (TCA, SSRI, beta-blockers, some antipsychotics, antiarrhythmics) must be taken into account since they may increase their plasma levels. Furthermore, the administration of drugs that may inhibit or be substrates of CYP2B6 may increase the plasma levels of bupropion and decrease those of its metabolite, although it is unknown if it has a clinical repercussion. The bupropion concentration may decrease or increase with the administration of enzyme inducers (carbamazepine, phenytoin) or enzyme inhibitors (valproate). It is necessary to take these factors into account when combining the drug.

DISCUSSION

Bupropion is a drug commonly used by the psychiatrist in the daily clinical practice as a combination strategy in resistant depressions, although it is also a drug of first choice in cases in which anergy and asthenia predominate in the picture. Due to its good tolerability, it is also used as an add-on to other antidepressants to minimize their side effects. Its absence of anticholinergic effects allows for its safe combination in elderly persons in patients with added neurological disease.

On the other hand, due to its dopaminergic effect and the implications of this neurotransmitter in the reward system, bupropion would be a good option in the population of depressed patients with comorbid substance usage.

It would be convenient to stress the aspects of bupropion such as its good profile of tolerability, limited effect in the sexual sphere and the fact that its action mechanism completely differs from the activity of the drugs used most, this being an added advantage of its combined use.

OPINION OF THE EXPERTS OF THE WORK GROUP

Prior to the writing of this chapter, the opinion of clinical psychiatrists on the use of bupropion in their daily practice was collected. The group was made up of 12 adult psychiatrists: 8 from the Mental Health Center, 1 from the Subacute Unit, 1 from the Outpatient Clinic of the General Hospital of adults and 2 from the Acute Unit of the Hospital General.

The group reported that their greatest experience was the use of bupropion in combination, generally added to a first therapeutic trial. Furthermore, the experts stressed those aspects that usually induce them to use bupropion with others psychopharmaceuticals.

1. Good strategy for resistant depressions.
The usual doses in the clinical practice of our country are between 150 and 300 mg, since these are the doses permitted according to the data sheet. However, experts feel safe using higher doses, of up to 450 mg. In the case of resistant depressions or residual symptoms, it is recommended to use full doses of each psychopharmaceutical (the concomitant use of bupropion and fluvoxamine is advised against due to the risk of seizures).
2. It avoids adverse effects in the sexual area and weight increase. In spite of the fact that we do not have literature that supports this opinion, in the experience of the group, the addition of bupropion makes it possible to use lower doses of SSRI and minimize the side effects of the latter.

Some of the experts have pointed out the utility of the combination of bupropion with mirtazapine or trazodone in the reduction of insomnia secondary to bupropion, it also being a good combination to potentiate the antidepressive effect.

In the clinical practice, in cases of patients with bipolar depression who do not respond to the use of mood stabilizers, the addition of bupropion is considered effective and having less risk than that of other drugs with a more noradrenergic profile.

This is a drug that can be used before initiating MAOIs or tricyclic antidepressants and, especially in case of apathy and abulia symptoms.

Finally, some of the experts reported having detected the following adverse effects on the psychopathological level in some cases: increased suspicion, manic symptoms and psychoticiform symptoms.

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