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Mirtazapine in combination

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Depression is undoubtedly a particularly important disease in terms of personal suffering and death as well as social, family, and economic costs. Pharmacological treatment is a reasonably effective therapeutic approach; however, a delayed therapeutic response and the persistence of depressive symptoms represent serious drawbacks to clinical recovery.

Although the pharmacological action of antidepressants begins a few hours after the start of treatment, an antidepressant response usually takes between 2 and 6 weeks.

The persistence of depressive symptoms after the first 6 weeks of treatment is indicative of a poor prognosis in terms of chronicity and a return to normal social function.

The combination of mirtazapine with other antidepressants may significantly lessen these drawbacks. Its antagonist effect on the presynaptic receptors reduces the latency of the antidepressant response. Moreover, its robust noradrenergic effect enhances the serotonergic effects of the most common antidepressants. In addition, the side effects of mirtazapine can be partially neutralized by the pharmacodynamic activity of other antidepressants, while mirtazapine can ameliorate the serious adverse effects, such as sexual dysfunction, of other medications.

Key words:
Mirtazapine, antidepressants, depression.

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La depresión es sin duda una enfermedad especialmente relevante en términos de sufrimiento personal, mortalidad y costes sociales, familiares y económicos. El tratamiento farmacológico supone un abordaje terapéutico razonablemente eficaz. Sin embargo el retraso en la aparición de la respuesta terapéutica y la persistencia de síntomas depresivos constituyen serios inconvenientes para la recuperación clínica.

Aunque la acción farmacológica de los antidepressivos se inicia a las pocas horas de iniciar el tratamiento, la respuesta antidepressiva suele demorarse entre dos y seis semanas.

La persistencia de síntomas depresivos después de las seis primeras semanas de tratamiento constituye un factor de mal pronóstico en términos de cronicidad y de una función social que no alcanzará la normalidad.

La combinación de otros antidepressivos con mirtazapina puede paliar de forma significativa estos inconvenientes. Su efecto antagonista sobre los receptores presinápticos reduce la latencia de respuesta antidepressiva. Por otra parte su robusto efecto noradrenérgico potencia los efectos predominantemente serotoninérgicos de los antidepressivos más corrientes. Finalmente los efectos secundarios de la mirtazapina pueden ser parcialmente neutralizados por la actividad farmacodinámica de otros antidepressivos, así como esta puede mejorar efectos adversos de otros medicamentos tan críticos como lo puede ser la disfunción sexual.

Palabras clave:
combinación de antidepressivos, potenciación (augmentation), depresión resistente, mirtazapina.

INTRODUCTION

Depressive disorders undoubtedly constitute a highly relevant disease group in social terms. The lifelong pre-

valence of depressive disorders in Spain ranges from 10 to 15% of the general population¹ and the risk of suicide among patients with depression is almost 15%. The 2:1 male:female predominance remains invariable in all study samples of patients with depression. Consequently, sample size is relevant.

Several aspects highlight the importance of this disease. On the one hand, the appearance of the anti-depressive response is habitually delayed by 2 to 6 weeks after the onset of treatment. On the other hand, at least one third of the patients who are correctly identified and adequately treated with monotherapy display complete therapeutic resistance. The implications in terms of personal suffering, disturbances in family dynamics, and work absenteeism are extremely notable.

Therapeutic response does not guarantee the complete recovery of the patient. Patient response is assumed to exist when the intensity of symptoms improves by 50%. However, if complete remission is not achieved, meaning that depressive symptoms persist, the risk of recurrence, relapse, or chronicity is very high, and this incomplete remission constitutes a form of partial refractoriness to treatment. Complete therapeutic remission is achieved in 35% of patients after a preliminary therapeutic test with monotherapy.^{2,3}

Consequently, further therapeutic measures have to be taken in almost two-thirds of patients treated with a single drug in the initial adequate treatment attempt (IAT). Changing to another drug may be the worst possible option because we can again expect weeks of delay before the patient starts to improve, with all the risks that this entails and only a 20% likelihood of success.⁴

In cost-effectiveness studies it has been shown that investing resources in increasing the intensity and means for the treatment of depression in order to minimize poor therapeutic response is economically beneficial, given the social dimension of depression and the ramifications of its persistence.⁵

DELAYED THERAPEUTIC RESPONSE TO ANTIDEPRESSANTS

The mechanism of action of all the antidepressants used in clinical practice is to enhance neurotransmitter traffic or availability. Most drugs act by blocking the serotonin (SERT) and/or noradrenaline (norepinephrine) transporter (NAT). This action involves an abrupt, massive increase in neurotransmitter in the extracellular space with the aim of coupling post-synaptic receptors and improving neurotransmission. However, although the first dose of antidepressant suffices to produce this action, the clinical effects manifested as an improvement usually take several weeks.

In effect, the extracellular increase in neurotransmitter concentration involves the cell bodies of the raphe nuclei, which results in massive stimulation of the somatodendritic autoreceptors. The mission of these autoreceptors is modulation, i.e., to repress neurotransmitter release, which results in diminished neurotransmitter release in the anterior brain.⁶⁻⁹ The clinical result not only is the initial absence of any therapeutic response; it is common for patients to present worsening of the nuclear symptoms of depression.

The sustained increase in extracellular neurotransmitter concentration and continuous stimulation of the autoreceptors produces down-regulation of these receptors, reducing their activity and definitively allowing increased synaptic transmission and thus facilitating therapeutic response.

Delayed therapeutic response or even disease exacerbation when antidepressive treatment is initiated is critical in a disease like depression because of patient suffering, the risk of suicide, and the health and occupational costs incurred.

It is not unusual that the most thoroughly tested therapeutic strategy for speeding up the therapeutic action of antidepressants is to antagonize the autoreceptors mentioned above.

The two neurotransmitters classically implicated in the pathogenesis of depression are serotonin (5HT) and noradrenaline (norepinephrine) (NA). The autoreceptors that modulate neurotransmitter release are, respectively, 5HT_{1A} and α_2 adrenoceptor. Pre-clinical studies of cerebral dialysis have made it possible to demonstrate that the addition of a 5HT_{1A} receptor antagonist, such as pindolol, can increase and sustain cortical serotonin release.^{6,10}

The use of a combination of antidepressants and pindolol is a therapeutic strategy that shortens the latency period of the antidepressive response, as has been demonstrated in several clinical trials,¹¹⁻¹⁴ especially in the first depressive episodes.¹⁵ The usefulness of this combination in depression refractory to specific drug treatment for depression does not seem as clear.^{6,17}

As for its antagonistic effect on the NA autoreceptor, the α_2 adrenoceptor, sufficient experimental and clinical evidence exists to support the usefulness of this therapeutic maneuver. The role of this receptor in the pathogenesis of depression offers little doubt. In effect, during active episodes of depressive disease, it has been demonstrated that the population of these autoreceptors increases, which is accompanied by a reduction in neurotransmitter release. When the depressive episode remits, receptor density returns to its original situation.¹⁸⁻²⁰ The antagonistic effect of α_2 adrenoceptors in preclinical studies enhances the action of antidepressant agents, including serotonergics.²¹ Effectively, on the one hand, the presence of α_2 heteroreceptors

in serotonergic neurons and, on the other hand, by means of direct stimulation through the activation of α_1 receptors, blockade of these autoreceptors increases the release of both NA and 5HT.²²⁻²⁴

The delay in the appearance of the antidepressive response can be shortened significantly. The use of drugs that antagonize the autoreceptors prevents the reduction in neurotransmitter release secondary to the abrupt increase in their extracellular concentration when amine reuptake is blocked by antidepressant drugs.

REFRACTORINESS TO ANTI-DEPRESSIVE TREATMENT: ABSENCE OF RESPONSE AND PERSISTENCE OF SYMPTOMS

The concept of resistant depression (RD) originated at the end of the 1960s, when the efficacy trials of imipramine and the tricyclic derivatives were completed. The term "resistant depression" refers to an episode of depression that has not shown sufficient improvement after treatment with a drug with demonstrated antidepressive activity in a sufficient dose and for an adequate time. From 30 to 40 % of patients do not respond after the first treatment and 5 to 10% fail to respond to more aggressive therapies.²⁵

On the other hand, in recurrent pathologies like depression, the factors that increase the risk of presenting new episodes should receive special attention. The failure to achieve remission and the persistence of symptoms are the primary factors that predict recurrence and progression to chronicity.²⁶ This means that the therapeutic intensity of depression is extremely relevant from the start. The prevention of chronicity and complete remission should be the therapeutic objectives.

Four groups of therapeutic strategies for treating antidepressive resistance exist: *a)* treatment optimization, which involves reviewing the diagnosis and ensuring compliance; *b)* the addition to or combination with the current treatment of substances that are not specifically antidepressants, such as lithium or thyroid hormone; *c)* change of the antidepressant, undoubtedly the least advisable option for the reasons noted above, and *d)* finally, the most common and least documented strategy: the association of antidepressants.

Based on the pharmacodynamics of the medications used to treat depression, a synergistic combination of two drugs should be guided by the principle of complementary drug action. This means that two drugs that act on different neurotransmission systems or through different and complementary mechanisms of action should be combined. The association of drugs for the same therapeutic objective

should adhere to these principles, which also results in a diversification of adverse effects.

Thus, in a patient being treated with a basically SSRI drug (selective serotonin reuptake inhibitor) who has an insufficient therapeutic response at 6 weeks, antidepressants with a fundamentally noradrenergic action, such as reboxetine²⁷ or mirtazapine^{28,29} could be added. From the perspective of mechanism of action, an SSRI acts by antagonizing the serotonin transporter (SERT), so it could be combined with a medication that, for instance, antagonizes autoreceptors.^{12,15,29} There is no sense in combining two medications that antagonize the same serotonin or noradrenaline transporter, or two medications that block the same 5HT1A or α_2 autoreceptors.

At present, there is little literature of quality on antidepressant associations, which should not surprise anyone. Most clinical trials examine efficacy and are undertaken by pharmaceutical companies for the purpose of registering a product and for the regulation of this process by health authorities (the FDA and EMEA regulatory agencies). Combination treatments address the needs of clinicians, so the sponsor of such clinical trials should be a private researcher or an organization linked to public research.

MIRTAZAPINE: INCREASES THE SPEED AND A MORE EXTENSIVE ANTIDEPRESSIVE RESPONSE

Primary pharmacodynamic action of mirtazapine and its effect on therapeutic response

Mirtazapine is an antidepressant with the primary mechanism of action of antagonizing α_2 noradrenergic autoreceptors. This maximally reduces the role of these synaptic structures in delaying antidepressive response. In addition, mirtazapine also has serotonergic effects that are mediated by the α_2 heteroreceptors located in serotonergic synapses and by the activation of 5HT firing through α_1 receptors, as was commented above.²²⁻²⁴

Clinically, this translates into more rapid action in relation to other antidepressants, such as both pure and dual SSRIs. Mirtazapine has been compared with citalopram,³⁰ fluoxetine,³¹ sertraline,³² paroxetine,^{33,34} and venlafaxine.^{35,36} Mirtazapine has also been observed to have more rapid action compared to other antidepressants in pool analysis.^{37,38}

Mirtazapine is thus an antidepressant with a dual effect, although its noradrenergic effect is stronger, which increments synaptic activity without affecting the amine transporter. Its primary mechanism of action is to antagonize the noradrenergic autoreceptor. The autoreceptor is responsible for the delay in the appearance of the antidepressant response.

Therefore, the pharmacodynamic profile of mirtazapine, which is basically noradrenergic and autoreceptor antagonistic, is ideal for combination with antidepressant medications that have a basically serotonergic or dual action, because mirtazapine adds a strong NA and autoreceptor-blocking properties to the current episode of refractoriness or partial response. These two properties are lacking in which other antidepressants available on the market.

Other pharmacodynamic actions of mirtazapine and their effect on tolerability

Mirtazapine is also a strong antagonist of the 5HT₂ and 5HT₃ serotonergic receptors.

These two actions have markedly positive effects in combination treatment of mirtazapine with other late-generation antidepressants. The antagonistic effect on the 5HT₂ receptor results in an enhanced anxiolytic effect and more efficient sleep since the REM phase is not suppressed, in contrast with what occurs with SSRI³⁹ antidepressants, which partly corrects one of the deficiencies of the drug with which mirtazapine has been combined.

On the other hand, blockade of the 5HT₃ receptor has effects on the digestive tract that can neutralize the adverse effects of digestive intolerance of SSRI or dual-neurotransmitter antidepressants, sometimes even completely, such as nausea, abdominal pain, and diarrhea. In effect, the strongest medications for the treatment of nausea secondary to drugs such as ondansetron or palonosetron primarily act through the mechanism of antagonizing the serotonin receptors.⁴⁰

Although we have less information about this pharmacodynamic activity of mirtazapine and sexual response, it is likely that blockade of the 5HT₃ receptor has a positive effect on the processes that regulate this activity. Although scant information is available on the role that the 5HT₃ receptor may have on a phenomenon as complex and multifactorial as the libido, some experimental findings are very suggestive. When male experimental animals are placed in the presence of receptive females, an increase in blood testosterone levels is detected. The use of drugs selective for different serotonin receptors suggests that such drugs can have a positive or negative effect on sexual activation. Ondansetron, a 5HT₃ antagonist, initially increases sexual hormone levels in these experimental animals, which allows us to hypothesize that the 5HT₃ receptor may be involved in the regulation of sexual response.⁴¹

Improvement of sexual response after the addition of mirtazapine to another antidepressant has been documented in the literature.^{42,43}

Mirtazapine's two actions on post-synaptic serotonin receptors would tend to neutralize or compensate for the most important adverse effects of the SSRIs or NSSRIs (dual-action SSRIs). This implies that mirtazapine has an added therapeutic value of improving the tolerability of the current antidepressant being used, in addition to potentiating the therapeutic action of the antidepressant and reducing the latency period until clinical improvement occurs.

Finally, mirtazapine has antihistamine effects and very weak anti-muscarinic effects, the last of which have no clinical consequences. The antagonist effect on H₁ histamine receptors suggests that mirtazapine may produce weight gain, basically by stimulating appetite. In effect, the possible weight gain is unrelated to glucose metabolism, as occurs with several second-generation antipsychotics,⁴⁴ and it is probably conditioned by a genetic polymorphism.⁴⁵ In any case, special attention should be given to advising significantly overweight patients about healthy lifestyles before starting mirtazapine treatment: low carbohydrate diets and regular exercise.

Pharmacokinetics of mirtazapine. Relevant aspects of the indication of the combination

Mirtazapine is absorbed rapidly and well when its two forms of presentation are administered orally, and it is not affected by the presence of food or other drugs. Mirtazapine reaches its maximum plasma concentration at two hours and has a half-life of 20 to 40 hours, which allows its administration in unit doses (preferentially at night due to its effect on sleep). A dosage of 30 mg/day produces plasma levels of 55 to 90 ng/ml once stable plasma levels are reached (the dosage should be reviewed in cases of poor tolerability). Mirtazapine has 85% plasma protein binding and is metabolized in the liver and eliminated by way of the urinary tract (80%) and stool.

Mirtazapine has linear pharmacokinetics. The clinical significance of this finding is that increases in dose produce proportional increases in plasma drug levels and are thus fairly predictable. The kinetics of mirtazapine is linear because it neither inhibits nor induces the enzymes that metabolize it in the liver. Mirtazapine is metabolized by three of the hepatic cytochrome (P450) isoforms present. CYP 2D6 and CYP 1A2 intervene in the hydroxylation and CYP 3A4 in the demethylation of mirtazapine.⁴⁶ Despite the fact that the effects of mirtazapine are irrelevant, as mentioned, other antidepressant medications with which it could be combined may significantly alter the activity of these enzymes.

Specifically, three of the most widely prescribed SSRIs are potent inhibitors of liver enzyme activity. Fluoxetine and paroxetine inhibit CYP 2D6, and fluvoxamine inhibits CYP

2C9 and 2C19. In contrast, carbamazepine, an alternative to lithium for the treatment of bipolar disorder, is a strong inducer of CYP 3A4.⁴⁷

Although this is not an absolute contraindication for these antidepressants, it means that the clinician must increase the level of control when mirtazapine is combined with fluoxetine, paroxetine, or fluvoxamine for a patient who is completely or partially refractory to monotherapy treatment. On the other hand, the use of these SSRIs should be avoided when the initial treatment is a combination treatment designed to shorten the response latency period.

Scientific evidence of the potentiation of antidepressants with mirtazapine

Since mirtazapine was introduced on the market, it has attracted the interest of many clinicians as an agent for potentiating antidepressants. Its peculiar mechanism of action meant that the autoreceptor desensitization period that precedes clinical improvement in depression could be avoided, while at the same time adding strong noradrenergic activity to the effect of the popular SSRIs on 5HT.

Carpenter et al.⁴⁸ reported on a series of 20 patients who had persistent depressive symptoms after standard treatment. Mirtazapine 15 to 30 mg/day was added to their treatment and 45% of them experienced an adequate therapeutic response within the first 2 weeks and 55% within 4 weeks. In this open-label study the authors pointed out that it would be interesting to corroborate these results in controlled studies.

The same group later communicated similar results in a randomized, double-blind, and placebo-controlled study. Twenty-six patients who did not respond to standard monotherapy treatment were randomized to receive mirtazapine 15 to 30 mg/day or placebo added to their ongoing treatment. At 4 weeks, the patients who were taking mirtazapine presented 64% therapeutic response and 45% remission compared to 20% and 13%, respectively, in the patients who received placebo; the tolerability was excellent.²⁸

Given the pharmacodynamic activity of mirtazapine, it is not surprising that its combination with dual-action antidepressants would attract interest. Venlafaxine, the first member of the group of dual-action serotonin selective inhibitors, is essentially an SSRI with a moderate noradrenergic effect. The combination of venlafaxine with mirtazapine produces an additional NA effect through a mechanism that reduces the latency period until therapeutic response. A first open-label study in which the association of mirtazapine and venlafaxine was used in refractory patients achieved excellent short and long-term results. The proportion of cli-

nical responses was 44% at 4 weeks and 50% at 8 weeks; response was maintained at 6 months. These percentages are no small matter considering that we are dealing with patients resistant to monotherapy. About 20% of patients experienced weight gain and drowsiness, but only 10% discontinued treatment due to poor tolerability.²⁹ These results were replicated in another study at the same time in which 81.8% therapeutic response and 27.3% remission were obtained in a sample of 22 patients resistant to monotherapy; the authors emphasized the excellent tolerability of the venlafaxine-mirtazapine association.⁴⁹

It is interesting to mention the use of mirtazapine in combination with SSRIs in stabilized patients who had sexual dysfunction secondary to their current antidepressive treatment. It is well known that sexual dysfunction, mainly diminished libido, is the most relevant adverse effect of treatment with SSRI, and the effect most often responsible for poor compliance. In this study, 30 mg/day (15 mg/day during the first week) of mirtazapine was added to the ongoing SSRI treatment in patients with secondary sexual dysfunction (25 women and 8 men). Half of the patients showed no problem of sexual response after 4 weeks of treatment. Despite the fact that the patients were stabilized, they showed a significant improvement in mood as confirmed by the Hamilton Depression scale.⁴² These results were replicated in a parallel study with duloxetine.⁴³

The study that definitively confirmed the role of mirtazapine in combination treatment was published by a group of the prestigious McGill University.⁵⁰ The sample consisted of 61 patients who presented an episode of major depression. The patients were randomized to three different treatment arms: mirtazapine alone, paroxetine alone, and an association of mirtazapine and paroxetine. The patients who did not respond to monotherapy after an increase in dose, in which none of the patients experienced improvement, were always switched in blinded mode to potentiation with the drug that they had not taken until then. This yielded comparative results of the two drugs, each in monotherapy, and the combination in terms of speed of action and magnitude of the antidepressive response. On the other hand, the second phase in which a second drug was added provided information about the capacity of the combination to treat refractory patients.

Although a difference in the reduction of the severity of symptoms was evident from the start in the combination treatment group, significant differences were found from day 35 of treatment. Of the patients who did not improve with monotherapy and an increase in dose, about 10 patients per treatment arm, 7 in the mirtazapine group and 5 in the paroxetine group improved. Of the 5 patients who did not improve in the combination group, all 5 improved after increasing the dose to 45 and 30 mg/day, respectively. At the end of the process and in accordance with the scoring

Table 1		Studies of treatment with mirtazapine combined with other antidepressants			
Authors	Design	Dose (mg)	Results	Highlights	
Open-label studies					
Carpenter et al., 1999	45 patients, reinforcement of current ATD in resistant MDD	15 - 30	45% response at 2 weeks; 55% response at 4 weeks	MIR effective in resistant depression. Tolerability should be studied.	
Hannan et al., 2007	32 patients resistant to monotherapy treated with VLF and MIR combination	15 - 30	44% response at 4 weeks; 50% response at 8 weeks	MIR combined with VLF was useful in patients resistant to treatment.	
Lopez-Muñoz et al., 2006	14 patients on treatment and MIR in combination	30 - 60	35% response; 28% remissions	Combination was effective. Good tolerability.	
Ozmenler et al., 2008	49 patients stabilized with SSRI who had sexual dysfunction	30	48.5% remission of sexual dysfunction and significant improvement in HAMD	MIR effective in the treatment of SSRI-induced sexual dysfunction. Additional clinical improvement. 4 to 8 week latency in improvement.	
Controlled studies					
Carpenter et al., 2002	26 patients resistant to monotherapy randomized to the addition of PLC or MIR	15-30	Therapeutic response: 64% MIR vs. 20% PLC	Significantly more responses and remissions with mirtazapine assoc	
Blier et al., 2009	61 patients, treatment of index episode, randomized to three arms: MIR, PRX and MIR + PRX.	PRX: 20 MIR: 30	Remission at six weeks: PRX: 26%. MIR: 19% PRX + MIR: 43%	Combination treatment produced a significantly faster response and a larger proportion of therapeutic responses and remissions.	
ATD: antidepresivos; TDM: trastorno depresivo mayor; VLF: venlafaxina; MIR: mirtazapina; RBX: reboxetina; PRX: paroxetina; PLC: placebo; ISRS: inhibidores selectivos de la recaptación de serotonina.					

criteria of the Montgomery-Asberg Depression Scale (MADRS), the percentage of therapeutic responses was 72% and of remissions, 54%.

This study demonstrated the superiority of the association of mirtazapine with SSRI compared to monotherapy in terms of both the speed and magnitude of the therapeutic response.

The studies supporting the superiority of associations with mirtazapine compared to monotherapy treatment are summarized in table 1.

CONCLUSIONS

As has been discussed, the two least favorable aspects of antidepressant treatment are the delay in the onset of improvement and the persistence of symptoms such as sleep disorders or cognitive difficulties, that can affect the long-term prognosis. The indication for associating mirtazapine with treatment contributes to palliating these two shortcomings. Although this study is limited by the possibilities of private researchers, there is enough scientifically sound evidence with a sufficient translational neurochemical basis to

support using mirtazapine combined with other dual-action or selective serotonergic antidepressants.

The use of the combination of drugs is conceptually justified when the aim is to enhance effectiveness or achieve a summation of therapeutic effects while diversifying undesired effects. The use of mirtazapine in combination with SRIs (selective reuptake inhibitors, dual-action or not), due to its antagonistic effect on the 5HT₃ receptor, neutralizes to a greater or lesser extent the adverse effects of these antidepressants, such as digestive symptoms and sexual dysfunction.^{42,43}

When mirtazapine is used in combination from the start, it is advisable to use SRIs that do not affect liver metabolism in order to minimize the risk of interactions. Despite the study by Blier et al.⁵⁰ cited, it is better not to use paroxetine, fluoxetine, or fluvoxamine because of the risk of interactions.

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