

Therapeutic Strategies in Treatment-Resistant Depression: Myths and Evidence



Laura Prieto-Arenas¹, Sofia Belló-Pérez¹, Laura Huerta-Melús¹, Sheila Fernández-Navarro¹, Raquel Brinquis-Seco¹ and M Carmen Arenas^{2*}

¹Hospital Obispo Polanco, Spain

²Faculty of Psychology, University of Valencia, Spain

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***Corresponding author:** M Carmen Arenas, Hospital Obispo Polanco, Av. Ruiz Jarabo, Faculty of Psychology, University of Valencia, Avda. Blasco Ibañez, 21, 46010 Valencia, Spain

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Short Communication

Treatment-resistant depression (TRD) is a challenge for psychiatrists. It is a disorder with a high prevalence, since approximately 30% of patients with depression do not respond to any treatment [1,2]. This may be due to two main factors, namely the union of several subtypes of depressive disorders and the coexistence of other psychiatric disorders [3]. Therefore, the diagnosis of TRD is complicated. Although there is no clear consensus among researchers to define diagnostic criteria of TRD [2-4], it appears that the most accepted definition is the non-response to two or more antidepressants at appropriate times and doses [5]. Due to the low consensus regarding the criteria for its diagnosis and the great variability of its evolution, on many occasions this pathology is diagnosed late and its treatment is very lengthy. This has a major impact on the patient's quality of life, constituting a major risk factor for suicide [6], and it also affects the global health economy.

Given the lack of response described, the introduction of adjuvant treatments is usually necessary, among which we can highlight the use of second generation antipsychotics, lithium or thyroid hormone [4]. Other possible non-pharmacological strategies include psychotherapy, transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) [7].

ECT, despite being a technique that has shown high effectiveness and speed in its performance in the management of TRD, is far from perfect. In many cases it requires sessions maintained over time, not relieving the patient of the risks posed by the use of general anesthesia. In addition, possible side effects to this technique include memory loss [8,9]. We cannot forget the stigma that accompanies it, derived from the bad press it has received in books, films and the media in the past. All this

means that on multiple occasions it outright generates rejection in patients and relatives. Other alternatives that are beginning to look promising are vagus nerve stimulation (VNS) and deep brain stimulation. However, more studies are needed to ensure their effectiveness [8].

Among the new therapies to consider with great preliminary results, we can highlight the use of intravenous ketamine and, more recently, intranasal esketamine [10,11]. However, although the compassionate use of ketamine/esketamine is a novel approach and increasingly more studies confirm its effectiveness in TRD, it should not be forgotten that it is an abuse substance and that, therefore, its administration may precipitate abuse or sensitization towards other drugs [12]. Thus, there is still some uncertainty about which step it should occupy in therapeutic algorithms. Studies indicate the need for repeated use or high doses [13], and at present, there are insufficient data on its long-term safety and tolerability [14].

The importance of different psychological therapies as adjunctive treatment should be emphasized. Although several studies indicate that no therapy is superior to another in its overall efficacy, all authors agree that it is a key element in the therapeutic approach of this disease. More studies are needed to determine which psychotherapy is most appropriate according to the characteristics of each patient [15].

In short, knowing the most suitable therapeutic strategy for each patient remains uncertain at present, since there is a lack of studies regarding the clinical, genetic and sociodemographic variables associated with therapeutic failure. It is necessary to emphasize the importance of having a good approach from the beginning by detecting the risk factors and characteristics of

the patient early, since when TRD is prolonged over time, the individual ends up accepting it as part of their identity and, consequently, it ends up adversely affecting their quality of life and their social and working environment.

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