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Psychiatric Psychobiological Treatment Versus Exclusive Psychological Treatment in Depressive Disorders

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Abstract: Introduction: Scientific information on the antidepressant effectiveness of the varied usual therapeutic interventions is considerable but of poor quality. Objective: To analyse the scientifically well qualified international contributions on the effectiveness of habitual psychobiological psychiatric interventions in depressive disorders. Method: N= 6 structured bibliographic systems have been reviewed in a non-systematic, narrative and synthetic way and N= 75 significant contributions have been selected. Results and discussion: Patients with severe depression are more likely to receive any type of medical attention, but less likely to receive adequate attention. The use of both drugs and psychotherapy is the habitual mixed combined intervention during any ordinary psychiatric treatment. We will call it psychobiological or psychopharmacological intervention. The exclusive psychological intervention without using any medically prescribed drugs, is likely to be less cost/effective. The matter is not only to prioritise but also to adequately combine psychiatric interventions and added psychological interventions when convenient. The intervention on the neurophysiological pathways related with glutamate, the GABAergic, opioidergic, and inflammatory systems as well as on connectome and microbiome are being promoted for future drug antidepressant therapy with encouraging results. Conclusion: The mixed psychiatric option using drugs and psychotherapy, either regulated or not, by the intervening psychiatrist himself or herself is probably the main therapeutic choice for the correctly diagnosed depressive disorders. The psychotherapeutics intervention excluding the psychobiological psychiatric intervention in correctly diagnosed depressions will be insufficient in general. The professional psychological intervention may obviously complement the mixed psychiatric intervention, but can not replace it.

Keywords: Depressive Disorder, Depression, Mini-Review, Psychobiology, Psychopharmacology, Psychotherapy, Treatment of Resistant Depression

1. Introduction

According to the World Health Organisation (WHO), depressive disorders affect 3.8% of the population, including 5% of adults and 5.7% of those over 60 years of age[1]. It is estimated that approximately 280 million people worldwide suffer from clinical depression. The WHO's "Comprehensive Mental Health Action Plan 2013-2030" emphasises relevant evidence-based psychosocial and pharmacological interventions and sets as one of its objectives the promotion of comprehensive, integrated mental health and social care services.

After a great deal of research, thousands of randomised clinical trials and billions of dollars/euros of funding, the size of the favourable effect of treatment compared to placebo for many mental disorders, including depressive disorders, is limited [1]. Antidepressant treatment may be the most usual in primary care and, mostly in specialised mental care. In the latter, only psychotherapy –use of psychological techniques– will be applied by clinical psychologists and psychopharmacotherapy will be applied by psychiatrist. When using "psychopharmacotherapy", which is the main and usual way of psychobiological treatment, we mean, here and from this point forward, the mixed use of drugs together with the implicit and inherent psychotherapic intervention that will usually accompany the medical prescription.

[1]https://www.who.int/news-room/fact-sheets/detail/depression

The aforesaid information, which is based on qualified studies involving more than 650,000 patients, does not invalidate or significantly spoil the positive findings obtained so far using antidepressant treatments. Since the estimated efficacy of a particular treatment depends on the comparator to which it is related, there is a tendency to prefer the comparison to be made with the standard treatment rather than with a placebo or waiting list. Treatment "as usual", as defined by Blais et al. (2013) [2], and as above mentioned, may also include psychotherapy –either implicit or explicit and also protocolised–, medication or a combination of the two when used routinely.

In this contribution, we aim to help to clarifying the value of the specific and scientifically endorsed use of psychopharmacotherapy, optimised for treating depressive disorders and preventing their recurrence. The objective of psychopharmacotherapy is to influence primarily the patient's cognition, emotion, mood, motivation and behaviour, and necessarily includes the usual psychotherapeutic interventions inseparable from the physician's prescription of medication, provided that he/she is a psychiatrist.

2. Method

Using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, more than nine out of ten care interventions that have been analysed in numerous recent Cochrane reviews are not supported by high quality evidence [3]. This includes the application of psychotherapies by psychiatrists and clinical psychologists.

GRADE provides practical principles for defining the quality of evidence, understood as the degree of confidence available that the estimate of an effect is adequate to make a recommendation. For this objective, which converges with that of evidence-based medicine, clinical practice guidelines developed by appropriate expert groups are essential, even if they are often criticised or questioned.

Primarily but not exclusively, in this contribution we have reviewed the following databases for psychopharmacological antidepressant treatment: 1) PUBMED, US National Library of Medicine, National Institute of Health; 2) Scientific Literature – SCILIT Indexing; 3) ÍnDICEs CSIC, for the Spanish Ministry of Science, Innovation and Universities; 4) American Psychological Association – PSYCINFO JOURNAL; 5) Excerpta Medica Data Base EMBASE – University of Kansas Medical Center; and 6) REDALYC Information System – Network of Scientific Journals from Latin America and the Caribbean, Spain and Portugal.

Many of the studies found were duplicated or highly similar, had poor quality or inadequate methodology, were included in a review already incorporated into the selected repertoire, or were too old. A common methodological problem was the method of diagnosis of clinically significant depression used in the studies and by whom. In the end, the count of recent research and other documents collected in this short, non-systematic, narrative and critical literature review is n= 75.

Below we will discuss, with reference to depressive disorders: 1) The use of psychopharmacological treatment as the main psychobiological intervention based on empirical evidence and duly endorsed by the scientific community; 2) The use of such treatment as an inseparable part of the psychotherapeutic activity inherent in any psychiatric intervention. Likewise, when it coexists with a coetaneous complementary properly psychological intervention, even if this is generalist or not specialised in nature; 3) The main use of markedly psychologistic or mentalistic interventions, as alternatives to medication alone or mixed interventions.

3. Results

3.1. Pharmacological Treatments for Depression

According to the WHO, people with major depression are more likely to receive any kind of care, but less likely to receive adequate care [4]. The combination of antidepressants appears to be superior to monotherapy and this advantage does not come at the cost of higher rates of serious adverse events. In particular, the addition of presynaptic α2 autoreceptor antagonists such as mianserin, mirtazapine or trazodone appears significantly more effective than other combinations [5].

On the other hand, serotonin-dopamine antagonist antipsychotics, known as atypical or second-generation antipsychotics, have been tested as an adjunctive drug alternative to antidepressant pharmacological treatment, although with limited quality of evidence [6]. In the USA, the prescription of antipsychotics has been restricted in recent years in the elderly with major depressive disorder (MDD) because of growing concerns about their adverse effects [7].

Commonly, for many mental and behavioural disorders, including affective disorders, combined treatment using psychopharmacotherapy and added explicit psychotherapy may be better than either option separately [8], although it is a fact that many people prefer the latter option without using the former. In any case, relatively little is known about which particular groups of patients may respond better to psychiatric treatment –using drugs and psychotherapy, which is generally informal– combined with psychological treatment –psychotherapy alone, either formal or informal– versus exclusive treatment, either drug alone or psychological alone [9]. Furthermore, there are substantial discrepancies in real life between clinical guideline recommendations and the actual use of medication [10].

For anxiety disorders, in the latest review conducted for German clinical guidelines, first-line medications include selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Among specific psychological interventions, cognitive behavioural therapy is the most beneficial. Since there is evidence in favour of combining explicit or implicit medication and psychological modalities, they should be initiated simultaneously [11]. The same is true for mood disorders.

Although the complexity and lack of precise knowledge about the pathophysiology of prevalent, heterogeneous depressive symptoms is challenging, psychopharmacological antidepressant treatment may be the most effective way to alleviate or cure symptoms in patients with MDD. However, beliefs in the usefulness or not of drugs prevail over evidence [12]. It has been proposed, albeit with limited scope for generalisation, that pharmacogenomics-based antidepressant treatment may become the best option for MDD in terms of effectiveness and tolerability [13, 14].

Poorly treated depression is predictably harmful especially in early adulthood. In a Finnish study, only 40.9% of depressed patients had received minimally adequate treatment, mainly due to delays in seeking help or premature discontinuation of the intervention [15]. For their part, it should be noted that older adults are less likely to report any perceived need for affective mental health care [16]. In any case, longer duration of untreated depression is associated with more severe cognitive impairment [17], to which we will return.

Impaired neurotransmission and disrupted signalling pathways may influence neuroplasticity involved in the dysfunction that occurs in depression. Aberrant neuroplasticity in the brain mediated by epigenetic dysregulation of gene expression can occur due to genetic and environmental factors. No doubt exists today of the high complexity of the many interrelated and basic neurophysiological pathways involved in depression.

It has been suggested that alterations in neurotrophins underlie the impaired neuroplasticity of depressive disorders. Consequently, future antidepressant drug development may need to be based on neurotrophin theory to enhance trophic signalling on neuronal and synaptic plasticity [18]. It is worth recalling that neuroplasticity refers to the brain's ability to adjust and reorganise itself flexibly in response to changing environments. Growth factors and associated neurotrophic signalling are also known to play an essential role in the development and maintenance of the central nervous system [19].

There is still no conclusive data on genetic links and depression. However, the S100A12, TIGIT, SERPINB2, GRB10 and LHFPL2 genes in peripheral serum have been identified as viable diagnostic biomarkers for depressive disorders, the first being the most valuable [20]. All five suggest changes in the immune system in clinical depression. Similarly, relevant biomarkers of rapid pharmacological antidepressant response have been identified, such as functional impairment of the brain connectivity networks of the limbic, cognitive and executive nodes.

Meta-analyses of neuroimaging studies establish a network of brain regions that is consistently altered in the large group of depressed patients, including the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex and insula, amygdala, hippocampus, basal ganglia, thalamus and cerebellum [21]. Grey matter density of the thalamus, in particular, has good potential as an aid in predicting individualised treatment response in patients with MDD [22]. The use of mathematical tools in network control theory in transcranial magnetic stimulation of electromagnetic pulse propagation as secondary electrical currents is being advocated [23].

There is growing evidence for the efficacy of neuromodulation techniques in improving the connectivity and neuroplasticity associated with depression. This is true, besides transcranial magnetic stimulation, of transcutaneous direct current stimulation, transcranial alternating current stimulation and photobiomodulation [24]. These technologies are continually proposed as possible alternative non-pharmacological approaches to treat unipolar depression and resistant depression.

There are also promising results on D-amino acid oxidase inhibition as a novel approach to perceived stress and cognitive impairment in patients with depression in old age [25]. D-amino acid oxidase is a flavoenzyme containing flavin-adenine dinucleotide (FAD) that catalyses with absolute stereoselectivity the oxidative deamination of all natural D-amino acids. FAD is a common cofactor of flavin, a flavin adenine dinucleotide-dependent mono-oxygenase, and is intended as a new measure of depression.

Depressive history has also been found to interact with allostatic load in predicting declines in cognitive performance. This load is a measure of the cumulative damage of physiological dysregulation that occurs from an early age as a result of chronic stress [26]. The theory of allostasis refers to the regulation over time of complex physiological processes, through the systemic response, to maintain its stability when facing physical, psychosocial or environmental changes and challenges [27]. Homeostasis will be maintained through the production of mediators such as adrenalin, cortisol and other chemical messengers.

3.2. Glutamate Receptors and Biomarkers

The above discussion of gene biomarkers helps to understand why glutamate-based therapy is a neurobiologically sound alternative to existing slow-acting pharmacotherapeutic options for clinical depression [28]. Due to the limitations of the predominant pharmacotherapy based on the monoamine hypothesis, glutamatergic pathways may offer an alternative and become a complementary option for designing new intervention strategies. It is worth recalling that glutamatergic neurons extend their action along the brain-medullary axis and that two thirds of the neurons in the cortex are glutamatergic.

There are already remarkable advances in understanding how glutamate modulatory actions impact on the so-called intrinsic connectivity networks of the human brain. Glutamate, a very abundant non-essential amino acid, is the main excitatory brain neurotransmitter, furthermore a metabolic and synthesis substrate, as well as an immune mediator. Since the 1990s, numerous investigations have consistently reported altered glutamate levels in MDD.

The GABAergic (γ-aminobutyric acid is the main inhibitory neurotransmitter), opioidergic and inflammatory systems are also being studied. See, for example: Aboul et al.

(2018) [29]. Pharmaceuticals that target the glutamatergic system include ketamine, an N-methyl-D-aspartate receptor antagonist, and esketamine, which is its enantiomer. Micro-RNAs, which are single-stranded ribonucleic acids, have also recently been found to play an important role in the development and progression of depression through the regulation of protein gene expression [30].

Although the data are very promising, there is a need for long-term non-inferiority double- or single-blind randomised controlled trials comparing the efficacy of repeated use of glutamate receptor modulators, such as the phencyclidine derivatives –ketamine and esketamine– mentioned above. Rigorous real-world monitoring is needed to gather comprehensive data on their safety and efficacy [31]. Ketamine, however, has not been shown to be significantly more effective in achieving remission of bipolar depression [32]. The evidence for the use of the remaining glutamate receptor modulators in clinical depression is rather limited.

The action mechanism underlying the rapid antidepressant effects of the glutamatergic agent ketamine in depressed patients, mainly in MDD, including resistant depression, remains unclear. A strong link has been suggested between improvements in mood and ketamine-induced increases in neuroplasticity, particularly with respect to intracellular signalling molecules [33, 34]. In any case, it is highly likely that many different pathways contribute to ketamine's antidepressant actions.

Neuroimaging research and studies of the *microbiome*[2], the latter of growing scientific interest, provide increasing evidence of glutamatergic dysfunction in clinical depression and other disorders. In particular, the gut microbiome and complex two-way gut-brain communication may affect behaviour and facilitate the development of depressive disorders, exacerbate their symptoms or contribute to their treatment and resilience [35]. Peptide hormones and gut bacteria in particular seem to be important in this interaction [36, 37].

Resistant depression is commonly understood as the subset of MDD that does not respond to traditional first-line treatment options. Currently, the most evidence-based therapeutic alternatives for resistant MDD are pharmacological augmentation strategies. Among the potentiating agents, second-generation antipsychotics and lithium carbonate have the strongest evidence for this ability [6, 38].

In children and adolescents, sertraline, escitalopram, duloxetine and fluoxetine are currently the only active substances formally recommended for first-line drug prescription in MDD. Furthermore, they may remain the main option in the future, despite the emergence of newer antidepressants [39]. Even with a paucity of high-quality evidence, fluoxetine alone, or in combination with cognitive behavioural psychotherapy, appears to be the best choice for the acute treatment of moderate to severe depressive disorder in children and adolescents [40, 41]. In adults with MDD all antidepressant drugs are more effective than placebo [42].

In the neuropathology of MDD, functional brain networks are damaged, resulting in relative cognitive impairment, as discussed above. The generalised dysfunctions of the brain's neural connections –or connectome– in patients with MDD include multiple large-scale encephalic networks [43]. The ultimate goal of any treatment is to achieve functional recovery, while the main component of practical deterioration in depressed patients occurs in psychosocial activity [44]. Changes in the organisation of the global network of structural and functional brain connectomes have been illustrated in MDD compared to healthy controls [45]. In general, it is now believed that functional network topology can become a powerful tool for depressive nosological diagnoses [46].

In line with what was said about biomarkers of glutamate-based therapeutics, brain neuroimaging values of the fractional amplitude of the low-frequency fluctuation, widely used in the study of neuropsychiatric disorders, may also be potential biomarkers to diagnose and differentiate patients with MDD or bipolar depression [47]. The best value as a neuroimaging diagnostic marker of the first episode of MDD has been the combination of: a) an increased fractional amplitude of the low-frequency fluctuation in the right precuneus –which forms part of the superior parietal lobe– and b) the increase of this amplitude in the left superior frontal gyrus [48, 49].

3.3. Psychobiological Psychiatric Treatment Versus Psychologistic Treatment

On a limited basis of randomised clinical trials, a number of authors conclude that exclusively regulated cognitive behavioural psychotherapy and second-generation antidepressants –integrated in habitual treatment– are viable options of similar efficacy for the initial treatment of MDD [50, 51]. In any case, the use of antidepressant drugs is quite safe for the treatment of these disorders [52], and their use in association with psychotherapy provided by the prescribing physician is common, considering Canada as an example [53].

A moderate body of evidence shows that regulated specific psychotherapy added to the usual adequate treatment –with antidepressants and implicit psychotherapy by the specialist physician– is beneficial for affective symptoms and for response and short-term remission rates in patients with resistant depressive disorders [54]. Note, however, that while guidelines and clinical practice directives are useful resources [55], many are poorly planned, reported and evaluated globally [56, 57].

That said, numerous studies suggest a better effect of formal and specific combined pharmacological and psych therapeutic therapy in chronic and severe MDD compared to less severe patients [58, 59]. Ongoing psychotherapy, in particular, may be more effective compared to no treatment in preventing depressive recurrences [60]. It is also worth considering the significant prevalence of comorbidities of

[2]Microbiome refers to the entirety of microorganisms, their genetic elements –genomes– and the interactions that they establish with the environment –epigenetics–.

alcohol abuse or dependence in depressions treated in outpatient mental health services [61], which is why maximum coordination is required among the various health care services involved [62].

Although MDD may be limited to a single episode in some patients, most patients will develop more or less severe recurrent symptoms over time [63], with a poor prognosis in the long run. Indeed, with broader outcome measures, such as including related mental disorders belonging to the mood spectrum, the course of clinical depression is found to be unfavourable and chronic for the majority of those affected.

In a recent nine-year long follow-up study, considering the presence of any disturbance of mood, anxiety or substance use as an outcome, the evolution of the disorder was quite negative [64]. The prominence of anxiety symptoms in depressed patients in remission is well established [65]. However, more than two-thirds of people who seek help for MDD eventually receive some antidepressant treatment that they themselves find helpful in their lives [66].

There has been speculation that so-called schema-focused cognitive therapy, a new integrating or "integrative" psychotherapy, is good for MDD, especially if combined with exposure and response prevention [67]. It has also been speculated that adding cognitive therapy to antidepressants can reduce suicidal ideation to a greater extent than medication alone [68]. But let us not forget that there is usually or should be a psychotherapeutic intervention implicit in the antidepressant pharmacological prescription, as there will always be if it is from a doctor specialising in psychiatry [69].

There remains very limited evidence on which to base the alleged relative effectiveness for depressive disorders in children and adolescents of the properly more psychological interventions, as well as the effectiveness of antidepressant medication alone and of the combination of both, which was pointed out years ago [70]. In adults, patients who do not respond to an exclusive pharmacological or psychotherapeutic treatment modality merit consideration for the addition of the alternative modality [71].

However, the latter authors [71] seem to be indifferent in their study to the carrying out of the sequence of both therapeutic modalities, which clashes head-on with expert clinical practice, which almost always prioritises the use of psychopharmacotherapy first in depressive disorders, with or without additional or complementary specific psychotherapy, despite the opinion of others, as stated at the beginning of this section [50, 51].

So-called "preventive cognitive therapy" has been proposed as an alternative to maintenance antidepressant drug treatment for recurrent depression. Adding it to antidepressant pharmacological treatment has been found to result in a reduction in the relative risk of recurrence [72]. However, the corresponding research was conducted with only antidepressant drug treatment as a comparator, not with the usual and full mixed psychopharmacological psychiatric treatment, in other words psychobiological treatment, so that the criticisms we made in this respect in the introduction of this article apply.

Let us also remember that from the legal and deontological perspectives, psychotherapeutic malpractice by psychiatrists, other doctors or psychologists can occur if the lex artis is breached [73]. Malpractice emphasises emotional or psychological harm caused negligently or culpably. The damage may involve any consequential impairment, damage, alteration or pathology. Interventions, and thus potential harm, may be due to errors in diagnosis, treatment choice, exclusivity or application. It should be noted that the respective recommendations in clinical practice guidelines are not equivalent to mandates, although they should be considered suitably [74, 75].

For Spain, among other laws, see General Health Law 14/1986 of 25 April 1986, as well as Basic Law 41/2002 of 14 November 2002, regulating Patient Autonomy, etc. See also Royal Spanish Decree 2490/1998 of 20 November 1998, which creates and regulates the official title of Specialist Psychologist in Clinical Psychology, as well as the University Code of Professional Psychology – General and Clinical, last amended on 21 October 2022.

4. Conclusions

While remaining a pragmatist, fallible and open scientific perspective, the choice for psychopharmacology, according to reliable indicators, is currently (and no doubt in future) in all probability the main cost-effective therapeutic option for depressive disorders. Disorders that are, of course, appropriately diagnosed using the criteria of DSM-5-TR®, American Psychiatric Association –codes 296.99 to 311– or WHO ICD-11®, with the corresponding codes 6A60 to 6A8Z. Both systematic, nosological and pragmatic consensus classifications should only be used by well-trained and competent medical or psychological practitioners.

Psychopharmacology in this article refers to the use of psychotropic drugs in relevant indications supported by scientific knowledge. In particular, its use is inseparable from the formal or informal psychotherapeutic practice that is inherent in any psychiatric intervention, so that the term includes both medication and psychotherapy. In the reasoned opinion of the author following this review, in depressive disorders, additional psychological help –which will usually be mainly added emotional, listening or supportive accompaniment– in coordination with psychobiological psychiatric treatment may be useful as a complement, not as an alternative.

No scientific mechanism, other than clinical trials, rigorously tests treatments to determine which works best in psychopathology and for whom. There are highly important interests in the pharmaceutical industry and various professional corporations that may influence the physicians' therapeutic choices. This is the case, for example, with some of the newer antidepressant drugs or with the considerable global pool of psychologists who are not adequately specialised in clinical psychology. In any case, it should be a priority to avoid poorly or undertreated clinical depression

because of its multiple and foreseeable adverse consequences.

Finally, comorbidity of residual relevant anxiety in depressed patients in remission is common and associated with poorer therapeutic outcomes. Recurrences, partial remissions and co-morbidities of various kinds are also common. It is therefore important that this is perceived and addressed by both professionals and relatives, furthermore by patients. In a considerable number of people, psychological support, with or without basic psychiatric treatment –that is, usually mixed with medication and concomitant psychotherapy– will have to be prolonged over time, as is the inverse case.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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