Review

Management of depressive disorder. What treatment should be use?

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Abstract

Throughout history, the human being has sought to improve and treat different mental pathologies, with advances in research, currently there is a wide variety of therapeutic options that can be a confounding factor when choosing the most appropriate treatment. This paper reviews the main treatment options for depression in order to provide guidelines that improve decision-making when addressing this pathology.

Key words: Depression, Antidepressants, Pharmacological treatment, non-pharmacological interventions.

Manejo del trastorno depresivo ¿Qué tratamiento elegir?

Resumen

A lo largo de la historia, el ser humano ha buscado mejorar y tratar las diferentes patologías mentales. Con los avances en investigación, actualmente hay una amplia variedad de opciones terapéuticas que pueden resultar un factor de confusión a la hora de escoger el tratamiento más adecuado para combatir el trastorno depresivo. Por tanto, en el presente trabajo se realiza una revisión de las principales opciones de tratamiento contra la depresión con el fin de brindar pautas que mejoren la toma de decisiones al abordar esta patología.

Palabras clave: Depresión, Antidepresivos, Tratamiento farmacológico, intervenciones no farmacológicas.

Introduction

Depression is an important public health problem, since it affects a large percentage of the population, increases morbidity and mortality, expenses related to medical care and generates a great impact on the functioning and well-being of patients. In the most serious cases it is related to suicide, which has enormous repercussions, since it is well known that suicide is a global phenomenon, which in 79% of cases occurs in low- and middle-income countries such as Colombia (1).

This disorder not only affects people who suffer from it, but also those who make up their close group. Its diagnosis and treatment is sometimes complex, because in many cases the symptoms can be confused or associated with other pathologies.

This article reviews the most recent definitions according to the fifth edition of the Statistical Manual of Mental Disorders (DSM) and the World Health Organization (WHO), since the main objective is to review the current pharmacological treatment of this disorder.

Epidemiology

According to the WHO, mental disorders have been increasing over the years, registering an increase of about 50% between 1990 and 2013 (416 million to 615 million).

Approximately 10% of the world's population suffers from a mental disorder, representing 30% of the global burden of non-fatal disease. The WHO indicates that more than 300 million people suffer from depression, of which a significant percentage depending on the intensity of the depressive picture, may present alterations in the family, school or work environment, currently being one of the first five disorders that generate greater disability and dependence. (2)

Another of the most relevant aspects is the association with suicide. Remembering that according to WHO data every year about 800,000 people die by suicide, and it is the second cause of death in the age group 15 to 29 years. (2)

Regarding the current situation in the country, the Depression Mental Health bulletin, published in 2017, records that there has been an increase in the care of patients with depression since 2009. The distribution of depression by age group shows that the cases seen increased as the age of the people increased, with a maximum point between 50 to 54 years of age and a new peak after 75 years. (3)

The 2015 National Mental Health Survey (ENSM) distributed the population according to age ranges, as follows: from 12 to 17 years old, from 18 to 44 and 45 years old and registered a higher prevalence of depression symptoms in adolescents and with respect to sex more in women with a ratio of 15 to 8. (3)

Definitions and possible causes.

The WHO defines depression as "the presence of sadness, loss of interest or pleasure, feelings of guilt or lack of self-esteem, sleep or appetite disorders, feelings of fatigue and lack of concentration" (2). For its part, the DSM-5, similarly describes that the presentation clinic can be constituted by the loss of interest or pleasure, a depressed mood most of the day or almost every day; somatic symptoms such as changes in eating habits, insomnia or hypersomnia, feelings of fatigue or loss of energy, cognitive symptoms such as impaired ability to think and concentrate. As well as thoughts of death and suicidal ideation. It specifies that the duration of symptoms must be at least two weeks and must represent a change from previous functioning (4).

It has been mentioned that depression can be associated with different medical conditions, especially serious pathologies such as a psychological reaction to the event. Other diseases such as cancer, especially pancreatic cancer in its initial stages, can manifest itself with depressive symptoms. In the same way, it has been related to respiratory, cardiovascular, neurological diseases such as dementias, epilepsy, multiple sclerosis, Parkinson's disease, as well as HIV-AIDS and endocrinological diseases such as hypothyroidism, Addison's disease, Cushing's disease and hypoglycemia among others.

Depression has also been linked to the use of some medications such as pain relievers, of which indomethacin is mentioned; antibiotics such as nalydixic acid, isoniazid, and sulfa drugs; antihypertensives such as clonidine, methyldopa, propanolol, and calcium channel blockers, as well as digitalis, corticosteroids, contraceptives, L-dopa and antipsychotics, especially the typical ones (5), (6).

Diagnosis

It is important to take a complete medical history, which chronologically describes the symptoms, the triggers, the pathological, pharmacological, toxic, allergic family history, etc. A complete mental examination and an exploration of the cognitive state should be carried out, since the findings can contribute to clarify the diagnosis. An important point in the evaluation of the patient is the evaluation of suicide risk, in which behaviors such as self-harm or passive behaviors such as abandoning the treatment of chronic diseases (5).

As for the complementary tests, they should be requested according to the diagnostic suspicion and aimed at ruling out the most common medical pathologies, for which the hemogram, urinalysis, electrolytes, glycemia, kidney function, transaminases, thyroid profile, HIV, serology, vitamin B12 levels and folic acid should be taken within the laboratory tests to consider (5).

Treatment

The main objective of the treatment is remission, control of symptoms and recovery of functionality. The 2013 Ministry of Health Guide (CPG) highlights the importance of determining the characteristics of the depressive condition to initiate management, whether pharmacological or not. These aspects to take into account are: the severity of the symptoms, the evolution time, the presence of previous episodes, their duration and the previous treatment received; Regarding the latter, it also establishes the relevance of knowing the degree of adherence that the patient has had, if they have presented adverse effects, if they present comorbidities and verify possible drug interactions (7).

Depending on the severity of the symptoms, psychotherapy is recommended as initial treatment in patients with mild depression, based on the criterion that the risk-benefit ratio, since drug therapy does not justify its use for mild symptoms. (7) (8). Also, when there is a contraindication to pharmacological management, such as in the case of pregnancy, lactation, complex medical illness with polypharmacy, the presence of interactions with other medications, a history of good response to psychotherapy in previous episodes, or a history of poor response to monotherapy with drugs. As well as in cases where there are triggers or alterations in the psychosocial context (bereavement, divorce, family or partner dysfunction, recent unemployment) (7) ,(8).

Regarding psychotherapy, the WHO defines it as "planned and structured interventions that aim to influence behavior, mood and emotional reaction patterns to various stimuli, through psychological, verbal and non-verbal means". Psychotherapy does not include the use of any biochemical or biological means. Many techniques and approaches, derived from different theoretical foundations, are effective in the treatment of

various mental and behavioral disorders ”(9). About the efficacy of psychotherapy, a meta-analysis of 25 studies, with 2036 patients, supports the additional value of psychotherapy, in combination treatment compared with pharmacotherapy alone for depression (10).

Cognitive behavioral therapy has shown positive evidence for both anxiety disorders and mild to moderate depressive disorder. This type of psychotherapy focuses on the relationship between thoughts, feelings and behaviors, with the aim of promoting in the patient the learning of better adaptive responses to stress other than emotionally negative responses. It should be noted that within this type of psychotherapy there are multiple elements and strategies used. For example, focus on problem solving, assertive training, cognitive restructuring, family communication training, relaxation, exposure, behavioral activation (11).

Rush et al. Conducted a prospective study regarding long-term results in patients with antidepressant treatment. The sample consisted of 3671 patients with depressive disorder, who showed improvement in their symptoms after a treatment combining: pharmacotherapy and psychotherapy. The subsequent follow-up, carried out for twelve months, allowed evaluating relapses and found a lower frequency of these in those patients who were with this combined therapy (12).

Another important aspect according to evidence-based medicine, but undervalued in the therapeutic arsenal, is the healthy lifestyle, as it has been shown to have positive effects in reducing and controlling depressive symptoms, even being considered as a protective factor. Recommendations in this regard include regular physical activity preferably daily, cessation of cigarette consumption, as well as reducing alcohol intake to 20 grams per day in men and half of it in women; in case of obesity or overweight, a weight reduction of 5% to 10%, an adequate sleep pattern between 7 - 9 hours a day in addition to adequate stress management and a positive attitude towards life (13).

Pharmacotherapy

With respect to drug treatment, there are various groups of antidepressants within which are:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SSRIs)
- Atypical antidepressants
- Serotonin modulators

The first generation, the oldest, are:

- Monoamine oxidase inhibitors (MAOI)
- Tricyclic antidepressants (TCAs)

There are different pharmacological options, however multiple studies show that the response does not vary much in terms of efficacy or speed of response; on the other hand, if it varies in terms of pharmacological properties, short-term and long-term side effects. Next, Table 1 lists the main drugs:

Table 1. ain drugs against depression. Starting dose, maximum dose and side effects:

Drug	Starting dose (MG)	Usual total dose per day - Extreme dose	Common adverse effects
Fluoxetine	20	20 to 60 – 80	Insomnia, agitation, sexual dysfunction, QTc prolongation, orthostatic hypotension, gastrointestinal toxicity
Sertraline	50	50 to 200 – 300	Insomnia, agitation, sexual dysfunction, QTc prolongation, orthostatic hypotension, gastrointestinal toxicity
Escitalopram	10	10 to 20 – 30	Insomnia, agitation, sexual dysfunction, QTc prolongation, orthostatic hypotension, gastrointestinal toxicity
Paroxetine	20	20 to 40 – 50	Anticholinergic, drowsiness, insomnia / agitation, orthostatic hypotension, gastrointestinal toxicity, QTc prolongation, increased weight gain
Fluvoxamine	50	50 to 200-300	Insomnia, agitation, sexual dysfunction, QTc prolongation, orthostatic hypotension, gastrointestinal toxicity
Citalopram	20	20 to 40	Insomnia, agitation, sexual dysfunction, QTc prolongation, orthostatic hypotension, gastrointestinal toxicity
Venlafaxine	37,5 to 75	75 to 375	Drowsiness, agitation, weight gain, QTc prolongation, sexual dysfunction
Desvenlafaxine	25 to 50	50 to 100 – 400	Insomnia, sexual dysfunction
Duloxetine	30 to 60	30 to 120	Insomnia, sexual dysfunction
Agomelatine	25	25 to 50	Less drowsiness, insomnia / agitation, sexual dysfunction.
Bupropion	150	300-400	Insomnia, QTc interval prolongation
Mirtazapine	15	15 to 45 – 60	Increased drowsiness, anticholinergic, QTc interval prolongation, weight gain, sexual dysfunction.
Trazodone	100	300 to 600	Drowsiness, QTc interval prolongation, orthostatic hypotension, sexual dysfunction.
Vortioxetine	10	20	Gastrointestinal toxicity, sexual dysfunction
Amitriptiline	25	150 to 300	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.
Nortriptiline	25	50 to 150	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.
Imipramine	25	150 to 300	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.
Desipramine	25	150 to 300	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.
Clomipramine	25	100 to 250	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.
Doxepine	25	100 to 300	Anticholinergic, orthostatic hypotension, QTc interval prolongation, sexual dysfunction, weight gain.

Tricyclic antidepressants and monoamine oxidase inhibitors have been among the oldest medications; However, due to their adverse effects and safety, they are not used as a first line.

It is recommended to start drug treatment in single or recurrent depressive episodes with moderate to severe severity and in mild cases when symptoms are persistent despite the use of other interventions such as psychotherapy, exercise or changes in lifestyle (7), (8). Pharmacological treatment in mild depression is considered only in certain situations, such as: patient preference, previous response to antidepressants or lack of response to non-pharmacological interventions (8).

Choice of antidepressant

Regarding drug therapy, some studies have questioned the efficacy of antidepressants, however, many studies support their efficacy compared to placebo. A meta-analysis of 37 randomized trials with 8,400 patients diagnosed with depression compared fluoxetine at doses of 20 mg per day or venlafaxine 75 to 150 mg per day, with placebo for six weeks; remission occurred in more patients who received active drug than placebo, which was 43% versus 29%. (14)

Taking into account the efficacy of antidepressants supported in the literature, the next step is to clarify which drug to choose.

The CPGs indicate as the first line of treatment for major depressive disorder: (SSRI) such as fluoxetine or sertraline, other antidepressants such as mirtazapine and amitriptyline; the latter is not recommended in older adult patients or in patients with contraindications for its use in those who suggest fluoxetine, sertraline or mirtazapine. (7).

As a second line of treatment, they recommend the use of first-line alternatives that they did not use among themselves: the other SSRIs, amitriptyline if not contraindicated, or mirtazapine.On the other hand, the Canadian guidelines (CANMAT) consider tricyclic antidepressants (TCAs), trazodone and an antipsychotic: quetiapine as second line; these drugs are placed in the second line of treatment due to the increased risk of side effects they present. They also consider other medications such as moclobemide and selegiline however they warn about possible serious drug interactions (7) ,(8).

Regarding the third line of treatment as options, the CPGs recommend: imipramine, clomipramine, paroxetine, escitalopram, citalopram, fluvoxamine, venlafaxine, duloxetine, desvenlafaxine, trazodone and bupropion; While the Canadian guidelines include MAO inhibitors, highlighting the higher burden of side effects and potential interactions with some foods and drugs, the latter appear as the fourth line of treatment in the CPGs (7), (8).

There are studies that have described that antidepressants differ in their effectiveness. A meta-analysis of 117 randomized trials comparing 12 second-generation antidepressants in nearly 26,000 patients with unipolar major depression found sertraline and escitalopram to be the drugs with the best efficacy and acceptability profile. Based on the reduction of initial symptoms ≥50% it was more likely with these, in addition to mirtazapine and venlafaxine, compared with paroxetine, fluoxetine and fluvoxamine (15).

In addition to taking into account the lines of treatment, in order to select an antidepressant, an individualized assessment of the needs of each patient and the profile of adverse drug reactions is always necessary.

It is necessary to consider the adverse effects of antidepressants, the main ones being: sinus tachycardia, hypotension, and cardiac conduction disturbances. Which are more related to tricyclic antidepressants, especially in older adults, in people with heart disease or in those with polypharmacy. Hypertension is also documented more often with dual antidepressants, especially with high-dose venlafaxine (7).

Sexual dysfunction occurs more frequently with selective serotonin reuptake inhibitors and dual antidepressants, indicating that the one with the highest risk is paroxetine, and the one with the lowest risk is bupropion. Regarding the presence of seizures, a slight increase in risk has been reported with TCAs, but they can also occur with high doses of bupropion (16).

Drowsiness occurs more often with trazodone, mirtazapine, agomelatine, and TCA. Gastrointestinal symptoms such as vomiting, nausea, diarrhea and hyponatremia with SSRIs, the latter especially in elderly patients (7), (16).

Gastrointestinal bleeding occurs more often with SSRIs, since they can inhibit platelet aggregation by altering platelet serotonin receptors, this risk is doubled with concomitant use of non-steroidal anti-inflammatory drugs and in older adults, so if they are formulated for people with a high risk of bleeding, the use of gastric mucosa protectors is recommended (7).

Urinary retention and dry mouth and eyes symptoms are more often evidenced with the use of tricyclic antidepressants, which is important to take into account in elderly patients or with rheumatological pathology in whom these symptoms may worsen (7)

Overdose toxicity can occur with everyone, but is much higher with tricyclic antidepressants and dual antidepressants. That is why it is recommended for people at high risk of suicide, another type of antidepressant as the first line in addition to taking precautions if it is necessary to prescribe them.

Elevation of liver enzymes is seen infrequently with most antidepressants. However, periodic liver function tests have been required for agomelatine because of the drug's potential to elevate liver enzymes (7) , (16)

Regarding possible drug interactions, the most relevant ones are generally caused by agents that are potent CYP inhibitors, such as fluoxetine (CYP2D6), paroxetine (CYP2D6), and fluvoxamine (CYP1A2, 2C19, and 3A4). Drug interactions with moderate CYP inhibitors, including bupropion, duloxetine, and sertraline (CYP2D6), are rarely clinically relevant except at high doses (16).

Treatment of depression and anxiety symptoms

In many cases this disorder has been associated with anxiety. Regarding treatment, high efficacy has also been evidenced in SSRIs, mainly paroxetine, sertraline, escitalopram and SSRIs.

Benzodiazepines are other effective medications used in the treatment of anxiety, as they lead to a reduction in emotional and somatic symptoms, in addition to limiting agitation in a matter of minutes. For their formulation, the risks of dependence and comorbidities of the patient must be taken into account, so they must be used with caution and avoided in patients with contact with psychoactive substances (11). Despite the rapid response, they are not the treatment of choice, they should only be considered as complementary treatment to SSRIs for a short time. Generally, they are started with low doses and are adjusted according to the patient's symptoms until their improvement. Reduction should be gradual with a dose decrease of approximately 10% over one to two weeks (17). Among the registered side effects of benzodiazepines, the following have been described: amnesia, hypokinesia, dependence, withdrawal symptoms, cognitive impairment and rebound anxiety.

There are other additional types of drugs used in the treatment of anxiety such as pregabalin whose mechanism of action described is the inhibition of calcium channels; how it works in anxiety disorder is unknown. It was approved in 2006 for the treatment of anxiety in Europe (17), but it is not approved for the United States; a relevant fact to consider is that they are better tolerated by patients than benzodiazepines. Its main side effects mainly include sedation and dizziness. (18)

Other treatment options

Another possible strategy is quetiapine, as mentioned, it is considered second-line in the management of depression; however, studies recommend its first-line use in geriatric depression, especially in patients with sleep disorders with doses that can fluctuate between 50mg to 300mg. In this regard, a double-blind controlled study in patients with depression treated with quetiapine had a significant reduction in MADRS scores and in the Pittsburgh sleep quality index compared to placebo (19). Similarly, several randomized clinical trials support the use of this atypical antipsychotic, although adverse effects such as sedation, weight gain, hyperglycemia, hyperlipidaemia, and extrapyramidal symptoms have been reported (18).

As new pharmacological options for the management of depression, management with ketamine has been included, which according to the evidence consulted, is recommended for patients with refractory unipolar depression, at a dose of 0.5mg / kg intravenously in 40 minutes, without achieving anesthetic effects . There are also studies with doses of 50mg intranasal and 0.1 to 0.5mg / kg intramuscular or subcutaneous. It is recommended to administer in a place with monitoring availability and a protocol must be created for its use. There is no evidence to recommend its long-term use (20).

In patients with persistent suicidal ideation or life-threatening behavior, electroconvulsive therapy (ECT) has been recommended; taking into account risks, adverse effects and non-acceptance by the patient. Pagnin D and colleagues discussed the efficacy of ECT in depression. Within one of the meta-analyzes they indicated that electroconvulsive therapy is more effective than any other treatment for severe major depression (21).

Conclusions

Currently, depression is a serious public health problem, which has great economic repercussions because it increases health care costs, as it increases morbidity and mortality and, in many cases, can lead to disability and dependence. In the most severe cases, it is associated with suicide, bringing with it multiple repercussions.

The treatment to be followed is determined according to the severity of the symptoms. In mild cases, psychotherapy is recommended as the first option, while in moderate to severe states, the use of drugs or combined therapy (medications and psychotherapy) is the indication. Cognitive behavioral psychotherapy has been shown to be more effective in treating depression.

There are multiple pharmacological options, despite which SSRIs are currently the first-line drugs in the management of depression due to their tolerance and safety. However, comorbidities, side effects and possible drug interactions must be taken into account.

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