Managing Major Depression:

A Review for the Busy Physician

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Major depressive disorder (MDD), which is characterized by the presence of at least one major depressive episode (MDE), is highly prevalent in the general population.[1] A worldwide survey carried out by the World Health Organization (WHO) suggests that the one-year prevalence of a depressive episode in the general population is 3.2%, while in primary care patients it increases to 5% to 10%.[2]

Unfortunately, despite its clear impact, MDD is often underdiagnosed and not adequately treated.[2,3]

The burden of MDD

MDD is associated with grave consequences in terms of excessive mortality, disability and secondary morbidity.[3] Indeed, according to the WHO, MDD ranked fourth in 1990 and will rise to second by 2020 in terms of the overall burden of all diseases in the world[4] and in terms of disability alone it ranked first in the 1990s.[5] Furthermore, in the US alone, depression accounts for > $43.7 billion in medical expenses and loss of productivity.[3]

MDD usually negatively influences the prognosis of a large number of medical conditions (*e.g.*, coronary disease, stroke, diabetes)[1-3] and patients' adherence to treatment.[6] Finally, it is commonly associated with other psychiatric disorders (*e.g.*, anxiety) and with suicidal behaviour.[6]

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Diagnosing a MDE

According to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV),[7] for a person to be diagnosed with a MDE, at least five of the following symptoms have to be present nearly every day during the same two-week period (or more) and these symptoms should impose a change from previous functioning:

- depressed mood,
- anhedonia (*i.e.*, markedly diminished pleasure in almost all activities),

- significant weight loss/gain,
- insomnia/hypersomnia,
- psychomotor retardation/agitation,
- fatigue or loss of energy,
- feelings of worthlessness or inappropriate guilt,
- diminished capacity to think or concentrate and
- recurrent thoughts of death or suicidal ideation.

Importantly, at least one of the symptoms must be depressed mood or anhedonia and the condition should not be secondary to a general medical condition, to substance abuse/dependence or to bereavement.

Managing MDD

The importance of establishing an appropriate treatment plan

An appropriate treatment plan for a MDD should take into consideration, among other things, patients' preferences and experiences with prior treatments, concurrent medications, concomitant psychiatric and/or physical ailments, the severity and/or subtype of the depression (*e.g.*, melancholic, psychotic) and suicide risk.[8-10] Importantly, an effective management plan should always be grounded on a strong therapeutic alliance.[2]

The treatment of a MDE usually proceeds in three distinct phases: acute (± three months), continuation (± six to nine months) and maintenance (± six to 24 months).[3] Acute treatment aims at achieving remission and continuation treatment is intended to prevent a relapse. Finally, maintenance treatment is aimed at preventing the onset of a new episode of depression after recovery and may be pursued from several months to a lifetime depending on the likelihood of recurrence.[8,9,11] As a practical rule of thumb, maintenance treatment for the first and second MDEs is kept for six months to a year, whereas after a third MDE, maintenance is frequently aimed at longer periods of time. However, when planning maintenance treatment, one needs to consider the individual patient's clinical history including factors such as the proximity of the depressive episodes, their clinical severity, past response to treatment, patterns of comorbidity and suicide risk.

Managing MDD in different treatment settings

A significant proportion of depressed patients can be successfully treated in primary care.[2] However, those with more severe illness should usually be referred to specialized (third-line) treatment (*e.g.*, individuals presenting with psychosis, active suicidality or with a condition deemed to be resistant to treatment or chronic).[2,8]

How to pharmacologically treat MDD

Robust evidence shows that antidepressants (*e.g.*, tricyclics, selective serotonin reuptake inhibitors [SSRIs], serotonin/norepinephrine reuptake inhibitors) are effective in treating moderate and severe MDD.[2,3,6,9,11,12] However, these drugs are usually not recommended for the initial treatment of mild depressions.[2] Benzodiazepines (*e.g.*, lorazepam) and atypical antipsychotics (*e.g.*, quetiapine) are commonly used along with antidepressants in

patients who have, for example, significant anxiety symptoms and/or insomnia.

Generally, SSRIs (*e.g.*, citalopram, sertraline) and other antidepressants (*e.g.*, venlafaxine, mirtazapine) are considered as first choice drugs for treating a MDE as they are usually better tolerated than, for example, older tricyclics (*e.g.*, amitriptyline, nortriptyline).[2,3,6]

Which antidepressant should be used first?

While, in principle, all antidepressants are effective, the clinician should decide among the different options based on the symptom profile of the patient and known side-effects of the different drugs. For instance, if the patient presents important anxiety symptoms, insomnia and significant loss of appetite, a good first option would be an antidepressant such as mirtazapine that is more sedative and that tends to increase appetite. A recent large meta-analysis comparing 12 new-generation antidepressants suggests that not all have similar efficacy and acceptability.[13] This study suggested that escitalopram and sertraline have the best profile of acceptability among all the different drugs tested.

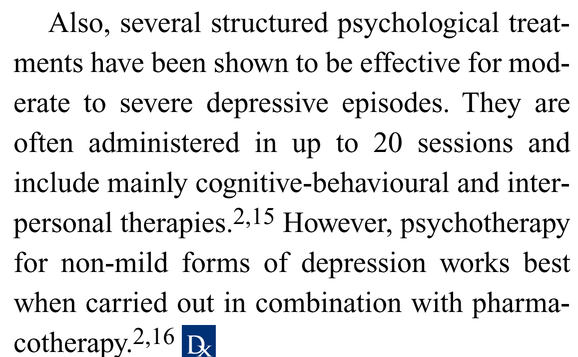
The response to pharmacological treatment must be carefully monitored (ideally through the use of patient self-reported and/or clinician-administered scales).[2] Also, patient's compliance with the therapeutics should be obviously ensured.[8] If there is only a partial or no clinical improvement after four to six weeks of an initial antidepressant treatment, then four different strategies may be employed:

- Optimization of the dosage and/or of the trial duration
- Augmentation of the antidepressant with a primarily non-antidepressant drug (*e.g.*, lithium, T3)
- Combination of antidepressants with complementary mechanisms of action (*e.g.*, adding bupropion to an SSRI)
- Switching to another antidepressant, preferentially with different mechanism of action (*e.g.*, from an SSRI to venlafaxine)[14]

Is psychotherapy recommended for treating a MDE?

Brief psychotherapeutic interventions (often administered in six to eight sessions) are usually recommended as first-line treatments for mild depressions.[15] They include guided self-help, problem-solving therapy, brief cognitive-behavioural therapy and counselling.[2]

Also, several structured psychological treatments have been shown to be effective for moderate to severe depressive episodes. They are often administered in up to 20 sessions and include mainly cognitive-behavioural and interpersonal therapies.[2,15] However, psychotherapy for non-mild forms of depression works best when carried out in combination with pharmacotherapy.[2,16] Dx



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