Antidepressant Therapy:
Making the Appropriate Choice

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The World Health Organization (WHO) predicts that by the year 2020, the prevalence of major depressive disorder (MDD) will be second to ischemic heart disease. The lifetime prevalence for MDD is 8%, while epidemiological studies continue to show that women have twice the risk of experiencing MDD and there is an alarming increase being reported in adolescents.

How is depression diagnosed?

Table 1 describes the diagnostic criteria for depression. Although the minimal duration of symptoms is two weeks, most patients have experienced these symptoms for several months before seeing a healthcare professional.

What is the treatment?

The most effective management for MDD is a combination of both non-pharmacologic and pharmacologic intervention. Psychotherapy, including cognitive-behavioural therapy (CBT) or interpersonal therapy, is effective in mild-to-moderate depression and should be used as adjunctive therapy along with antidepressants in more severe depressions.

Gordon's case

Gordon, 47, has been experiencing:

- decreased sleep for the past 2 to 3 weeks,
- decreased energy,
- a loss of appetite,
- depressed mood for several months and
- anxiety at work.

He is diagnosed with depression and is started on fluvoxamine.

Questions

1. Why is a more sedating antidepressant prescribed for Gordon?
2. Are there any non-pharmacologic therapies that could be suggested instead?

Follow-up

Gordon's sleep, appetite and anxiety have improved but his mood is still not back to normal. Since he displayed a partial response, a decision is made to augment his therapy with 600 mg of lithium b.i.d. Two weeks later, Gordon reports that his mood has improved but he has trouble tolerating the tremors and dry mouth from lithium.

Lithium is discontinued and the fluvoxamine dose is decreased by 50 mg every few days until he reaches 50 mg q.d. Venlafaxine, 37.5 mg, is started and fluvoxamine is discontinued. The dose is increased eventually to 150 mg and Gordon's depression continues to improve.

Table 1

Diagnosis of major depressive disorder[1]

Depression is present if ≥ 5 of the following symptoms have occured during the same 2-week period; at least one is either:

- Depressed mood, OR
- Loss of interest or pleasure

Besides the first 2 symptoms, patients can experience:

- Weight disturbance
- Fatigue or loss of energy
- Psychomotor agitation/retardation
- Insomnia or hypersomnia
- Feelings of worthlessness or guilt
- Difficulty concentrating
- Suicidal ideation

Symptoms cause significant distress leading to impaired functioning and are not the result of medical disorders, substance/drug abuse or bereavement. Moreover, they are not associated with mania/hypomania.

Along with patient interviews, diagnosis can be aided by the use of rating scales:

- Hamilton Depression Rating Scale
- Beck Depression Inventory
- Montgomery-Asberg Depression Rating Scale

How do you select an antidepressant?

Based on safety and efficacy evidence, first-line agents include all the selective-serotonin reuptake inhibitors (SSRIs) as well as the novel agents venlafaxine, mirtazapine and bupropion.

Tricyclic antidepressants (TCAs), which may be more effective than SSRIs in depressed hospitalized patients, are considered second-line therapy because of their potential fatal outcome in overdoses.

The traditional monoamine oxidase inhibitors (MAOIs), which require dietary restrictions, are third-line agents, while moclobemide, a reversible MAOI agent, can be used as second-line therapy.

The selection of an antidepressant will depend on the:

- symptoms of depression,
- antidepressant properties,
- presence of comorbid psychiatric disorders,
- concomitant medications,
- previous good response and tolerability as well as
- cost of the medication.

Table 2 lists the recommended dosages for the commonly-prescribed antidepressants.

• FAQ •

When switching antidepressants, how long should I wait?

The initial antidepressant should be tapered to its lowest dose and a new agent can be started at its lowest dose. If switching to a traditional monoamine oxidase inhibitor, a washout period of 5 half-lives of the initial drug is needed.

• FAQ •

Do antidepressants cause suicidal ideation?

Strong evidence linking suicidality with antidepressants in adults is lacking but there may be a slight risk in children and adolescents. Initiating treatment remains a significant period of risk for suicidal behaviours and should be closely monitored in all patients.

Q&A *So, the first trial failed. What to do next?*

Clinical trials typically report response rates of 50% to 60% (defined as a 50% reduction in symptoms) and remission rates (almost complete response) of 35% to 40%.

Several options are available if a patient has not responded to the antidepressant despite an adequate trial, therapeutic dose, tolerability, ensuring compliance and the assessment for substance abuse. The first step is optimizing the dose. SSRIs demonstrate a dose response curve which is flat, meaning the majority of patients will respond to a low dose. However, higher doses may be necessary for severe depression and those with comorbidities.

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No response

If the patient has not shown any response, it is better to select a different antidepressant and preferably from a different class. Switching to a different SSRI will result in only a slight improvement. Patients failing two SSRIs should be switched to a different class. Continuing monotherapy minimizes the chances for drug interactions, additive side-effects and cost to the patient.

The WHO predicts that by the year 2020, the prevalence of MDD will be second to ischemic heart disease.

Partial response

If the patient has shown a partial response, augmenting the antidepressant with either 750 mg to 1,200 mg of lithium q.d (serum levels of at least 0.5 mmol/L) or 25 µg to 50 µg of triiodothyronine is an option. Augmentation therapy should be discontinued in three to four weeks if there is no response. Some recent studies have reported benefits when SSRIs are potentiated with either:

- lamotrigine,
- buspirone,
- pindolol, or
- olanzapine.

Alternate options

For patients who have failed two or three antidepressant trials or continue to show only a

Table 2
Dosages for commonly-prescribed antidepressants

	Starting dose	Standard dose
SSRIs		
Citalopram	20 mg	20 mg-40 mg
Escitalopram	10 mg	10 mg-20 mg
Fluoxetine	10 mg	20 mg-60 mg
Fluvoxamine	50 mg	100 mg-300 mg
Paroxetine	10 mg	20 mg-40 mg
Sertraline	25 mg	50 mg-150 mg
Novel agents		
Bupropion	100 mg	150 mg-300 mg
Mirtazapine	15 mg	15 mg-45 mg
Venlafaxine	37.5 mg	75 mg-375 mg

SSRIs: Selective serotonin reuptake inhibitors

partial response at optimal dosage, options include trying a TCA if the patient is not suicidal, then either a traditional MAOI (tranylcypromine, phenelzine) or combining two antidepressants with different neurochemical properties, such as a SSRI or venlafaxine with bupropion or mirtazapine.

• FAQ •

Which antidepressant, if any, can be prescribed in children and adolescents?

Health Canada has not approved any antidepressants, while the FDA has approved fluoxetine. Sertraline is considered to be second-line therapy while tricyclic antidepressants, unlike fluoxetine, have not been shown to be safe or effective.

Treatment-resistant alternatives have been mostly reported from small non-comparative trials using TCAs. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study attempted to strengthen the evidence by providing timely medication alterations (switching, augmentation, combination, CBT) when remission was not achieved. Unfortunately, the study failed to demonstrate any superior treatment options.

Q&A *What are standard phases and trial durations?*

An adequate trial varies from four to six weeks; perhaps longer in the elderly. Patients should be monitored every one to two weeks during initial therapy. Except for the more sedating agents (fluvoxamine and mirtazapine), all

Take-home message

- The most effective management for depression is a combination of psychotherapeutic and pharmacologic therapies
- Non-compliance (social stigma, adverse effects, cost) and substance abuse are common causes for patients not responding to antidepressant therapy
- The total treatment period for a first episode of major depression should be one year
- When discontinuing antidepressants, all should be tapered over several weeks to minimize withdrawal symptoms

antidepressants should be prescribed in the morning to minimize the possibility of insomnia. Somatic symptoms, such as sleep and appetite, generally improve early in therapy followed by improvements in energy and pleasure. During this later phase, patients should be carefully assessed for any suicidal ideation. Mood will continue to improve while full remission will take eight to 12 weeks.

Most patients have experienced symptoms of depression for several months before seeing a healthcare professional.

It is recommended that the total treatment period for a first MDD episode should be one year. Relapses occurring within five years should be subsequently managed for an additional one to two years, while a third relapse or high risk patients (*i.e.*, dysthymia, psychotic depression) may require indefinite treatment.

How to discontinue antidepressants?

The abrupt discontinuation of long-term antidepressants can lead to withdrawal symptoms described by the acronym FINISH:

- Flu-like
- Insomnia
- Nausea
- Imbalance
- Sensory disturbance
- Hyperarousal

All antidepressants should be tapered gradually over at least a two week period, if not longer. If symptoms are intolerable, re-initiate therapy and titrate slower. Dx

Resources

1. *Diagnostic and Statistical Manual of Mental Disorders.* Fourth Edition. (Text Revision). American Psychiatric Association, Washington DC, 2001.
2. Mann JJ: The Medical Management of Depression. N Engl J Med 2005; 353(17):1819-34.
3. Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments (CANMAT): Clinical Guidelines for the Treatment of Depressive Disorders. Can J Psychiatry 2001; 46(Suppl 1):5S-90S.
4. Rush AJ, Trivedi MH, Wisniewski SR, et al: Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. Am J Psychiatry 2006; 163(11):1905-17.