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A brief overview on depression and its treatments

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Abstract
Some drugs used for long periods, such as prednisone, certain blood pressure medicines, sleeping pills, antibiotics and even birth control pills in some cases, can cause depression or make an existing depression worse. Some antiseizure medications, like Lamictal (lamotrigine), Topamax (topiramate), and Neurontin (gabapentin), may be associated with a higher risk of suicide.

Keywords: depression, drugs, treatment, adverse effects

Introduction
Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850 000 lives every year. Depression is the leading cause of disability as measured by YLDs (Years Lived with Disability) and the 4th leading contributor to the global burden of disease (DALYs-Disability Adjusted Life Years) in 2000. By the year 2020, depression is projected to reach 2nd place of the ranking of DALYs calcuated for all ages, both sexes. Today, depression is already the 2nd cause of DALYs in the age category 15-44 years for both sexes combined. Depression occurs in persons of all genders, ages, and backgrounds.

Diagnosis
Currently, no laboratory test can be used to diagnose depression. Depression is diagnosed based on your reported symptoms, signs that your doctor observes while interviewing you, your medical history and your family's medical history. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is used in making the diagnosis. According to the *DSM-IV*, a person who suffers from major depressive disorder must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period. This mood must represent a change from the person's normal mood; social, occupational, educational or other important functioning must also be negatively impaired by the change in mood. A depressed mood caused by substances (like drugs, alcohol, medications) or which is part of a general medical condition is not considered to be major depressive disorder. Major depressive disorder cannot be diagnosed if a person has a history of manic, hypomanic, or mixed episodes (e.g., a bipolar disorder) or if the depressed mood is better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreni form disorder, delusional disorder or psychotic disorder.

Symptoms and signs
The symptoms should not be accounted for by another illness, drugs of abuse or prescription medications.

Common symptoms of depression are as follows:

a. **Depressed Mood:** A person may report feeling "sad" or "empty" or may cry frequently. Children and adolescents may exhibit irritability.
b. **Decreased Interest or Pleasure:** A person may show markedly diminished interest or pleasure in all, or almost all, daily activities.
c. **Weight Changes:** Significant changes in weight when not attempting to gain or lose (a gain or loss of 5% or more in a month) may be indicative of depression. In children, this may also present as a failure to make expected weight gains.
d. **Sleep Disturbances:** Insomnia or sleeping too much may be a symptom of depression.

Psychomotor Agitation or Retardation
The person may be observed to be either agitated or restless or physically slowed down in their movements. F. Fatigue: Deep fatigue or a loss of energy is a symptom of depression. G. Feelings of Worthlessness or Guilt: A depressed person may feel that they have no value or they may feel inappropriately guilty about things they have no control over. H. Brain Fog: A depressed person may have a diminished ability to think, concentrate or make decisions.

Thoughts of Death
A depressed person may have recurring thoughts of death, especially thoughts of suicide, with or without a specific plan.

Causes of Depression
The causes of depression are complex. Genetic, biological, and environmental factors can contribute to its development. In some people, depression can be traced to a single cause,

while in others; a number of causes are at play. For many, the causes are never known. Currently, it appears that there are biochemical causes for depression, occurring as a result of abnormalities in the levels of certain chemicals in the brain. While we still don't know exactly how levels of these neurotransmitters affect mood, we do know that the levels can be affected by a number of factors. Monoamine hypothesis of depression has been shown in Fig. 3.

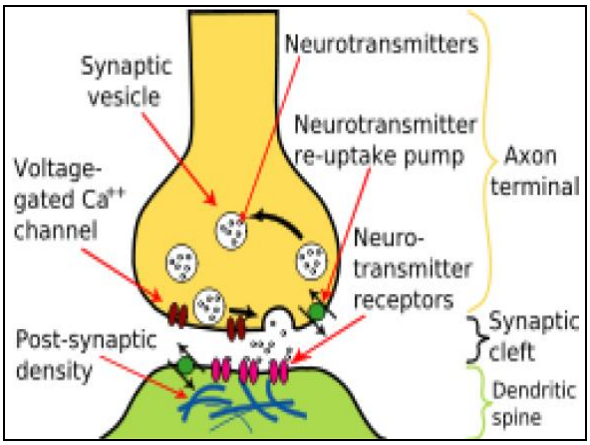

Fig 1: Monoamine hypothesis of depression

1. **Heredity:** Certain types of depression seem to run in some families. Research is ongoing as to exactly which genes are involved in depression. Just because someone in your family has depression, however, doesn't mean you will. Sometimes, family members who were known to abuse alcohol or other drugs were unwittingly trying to improve their mood (often called "self-medication" by professionals).
2. **Personality:** People with certain personality traits are more likely to become depressed. These include negative thinking, pessimism, excess worry, low self-esteem, a hypersensitivity to perceived rejection, overdependence on others, a sense of superiority or alienation from others, and ineffective responses to stress.
3. **Situations:** Difficult life events, loss, change, or persistent stress can cause levels of neurotransmitters to become unbalanced, leading to depression. Even major happy events, such as childbirth, can cause changes in hormone levels, be stressful and cause clinical depression, as in postpartum depression.
4. **Medical conditions:** Depression is more likely to occur with certain medical illnesses. These "co-occurring" conditions include heart disease, stroke, diabetes, cancer, hormonal disorders (especially perimenopause or hypothyroidism, known as "low thyroid"), Parkinson's disease, and Alzheimer's disease.
5. **Substance abuse:** While it has long been believed that depression caused people to misuse alcohol and drugs in an attempt to make themselves feel better (self-medication), it is now thought that the reverse can also be the case; substance abuse can actually cause depression.

Types of Depression

There are several different types of clinical depression (mood disorders that include depressive symptoms):

A. Major depression

It is an episode of change in mood that lasts for weeks or months. It is one of the most severe types of depression. It usually involves a low or irritable mood and/or a loss of interest or pleasure in usual activities. It interferes with one's normal functioning and often includes physical symptoms. A person may experience only one episode of major depression, but often there are repeated episodes over an individual's lifetime.

B. Dysthymia

It is less severe than major depression but usually goes on for a longer period, often several years. There are usually periods of feeling fairly normal between episodes of low mood. The symptoms usually do not completely disrupt one's normal activities.

C. Bipolar disorder

It involves episodes of depression, usually severe, alternating with episodes of extreme elation called mania. This condition is sometimes called by its older name, manic depression. The depression that is associated with bipolar disorder is often referred to as bipolar depression. When depression is not associated with bipolar disorder, it is called unipolar depression.

D. Seasonal depression

Which medical professionals call seasonal affective disorder, or SAD, is depression that occurs only at a certain time of the year, usually winter, when the number of daylight hours is lower. It is sometimes called "winter blues." Although it is predictable, it can be very severe.

E. Psychotic depression

It refers to the situation when depression and hallucinations or delusions are experienced at the same time (co-occur). This may be the result of depression that becomes so severe that it results in the sufferer losing touch with reality. Individuals who primarily suffer from a loss of touch with reality (for example, schizophrenia) are thought to suffer from an imbalance of dopamine activity in the brain and to be at risk of subsequently becoming depressed.

Antidepressants-treatment

There are several treatments available. Medications and psychotherapy either alone or in combination--are the most common forms of depression treatment. ECT and VNS are generally only administered when other treatments have failed or when medication might endanger the patient's health. Your doctor can help you select the best depression treatment for you. The terms "refractory depression" and "treatment-resistant depression" are used to describe cases that do not respond to adequate courses of at least two antidepressants [1].

Medications

The first-line treatment for depression is an antidepressant, as studies show these drugs help a significant number of people experience complete remission, or at least significant

improvement, in their symptoms. The most-studied form of psychotherapy for depression is Cognitive behavioural therapy (CBT), which teaches clients to challenge self-defeating, but enduring ways of thinking (cognitions) and change counter-productive behaviors. Research beginning in the mid-1990s suggested that CBT could perform as well or better than antidepressants in patients with moderate to severe depression [2]. CBT may be effective in depressed adolescents [3], although its effects on severe episodes are not definitively known [4]. Combining fluoxetine with CBT appeared to bring no additional benefit or, at the most, only marginal benefit [5]. Several variables predict success for cognitive behavioral therapy in adolescents: higher levels of rational thoughts, less hopelessness, fewer negative thoughts, and fewer cognitive distortions [6].

Counseling and Psychotherapy

Psychotherapy is a process in which a trained professional enters a relationship with a patient for the purpose of helping her with mental illness, behavioral problems, or personal growth. The process involves the patient and therapist sitting in a room talking, which is why it is often called "talk therapy." Psychotherapy is thought to be most effective for depression when used in conjunction with medication. "Psychotherapy" and "counseling" are often used interchangeably. However, in the context of mental health, counseling generally refers to a relatively brief treatment that is focused mostly upon behavior.

Electroconvulsive Therapy

Electroconvulsive therapy, also known as ECT, is a form of treatment for depression that involves the application of a brief electrical pulse to the scalp in order to produce a seizure. ECT might be administered when medications have not been effective, when medications might endanger the patient, or when a rapid response is needed.

Vagus Nerve Stimulation

Vagus nerve stimulation, or VNS, involves the use of an implanted device to provide periodic stimulation to the vagus nerve. The device was originally developed as a treatment for epilepsy. It has since been approved for treatment-resistant depression in both unipolar depression and bipolar disorder.

Mothers and Their Children

Mothers and children will face special treatment issues, especially regarding the safety and effectiveness of particular treatments. Pregnant and breast-feeding women must balance their own mental well-being against the needs of their baby. Mothers also have concerns about whether antidepressants are safe for their older child to use.

Antidepressants

Iproniazid, the first modern antidepressant, was originally developed as an antituberculosis drug in the early 1950s. In addition to its ability to treat tuberculosis, iproniazid was observed to elevate mood and stimulate activity in many patients. The introduction and use of the *Rauwolfia* to treat psychiatric disorders. The iproniazid to treat the symptoms of depression. After promising preliminary findings reported in 1957, iproniazid was prescribed widely to patients with major depression. Thus, monoamine oxidase inhibitors (MAOIs) were developed at the end of the 1950s. By blocking the action of oxidases which break down neurotransmitters in the brain, it is possible to "bath" brain in large quantities of neurotransmitters, and to fight off the depression. The first tricyclic antidepressant, imipramine, was originally developed in a search for drugs useful in the treatment of schizophrenia. The therapeutic and commercial success of substituted phenothiazines such as promethazine, promazine, and chlorpromazine, initiated an enormous effort in the molecular modifi cation of the polycyclic phenothiazine ring structure and its *N* -aminoalkyl side chain. After a while, a substance was unearthed, iminodibenzyl. It was not a new drug. Iminodibenzyl had been discovered in 1898 and used briefly as an intermediate, in the preparation of Sky Blue, a dye stuff. Iminodibenzyl, however, had a tricyclic ring structure, similar in appearance to the phenothiazines. Derivatives of iminodibenzyl where the sulfur bridge of the phenothiazine ring of promethazine is replaced with an ethylene bridge, they produced 42 separate basic alkylated derivatives, each being distinguished only by slight differences in their side-chains. Among the new molecules, they synthesized *N*-(dimethylaminopropyl)-imino-dibenzyl, which came to be called imipramine, a weak antihistaminic and mild anticholinergic with sedative properties in normal human volunteers. Although clinical trials demonstrated a lack of effect in treating schizophrenia, to examine its effectiveness in depressed patients, Some 500 patients with various psychiatric disorders that were treated, only those with endogenous depression with mental and motor retardation showed a remarkable improvement after about 1-6 weeks of daily imipramine therapy. "They again become interested in things, are able to enjoy themselves, despondency gives way to a desire to undertake something, despair gives place to renewed hope in the future," Kuhn wrote. These effects led to the idea that imipramine was selectively reversing the depression, rather than simply producing a general activating effect [7, 8]. Subsequent biochemical studies on imipramine demonstrated that this drug increased the activity of the monoamine neurotransmitters, norepinephrine, and serotonin, by preventing the reuptake [9]. It did not take long for the diamine structure of an additional secondary amine group in imipramine to be substituted with an ethylene group in amitriptyline. It was another tricyclic antidepressant subsequently widely used. Understanding of the activities of these drugs, in combination with other observations, provided the foundation for the monoamine hypothesis of depression, which proposes that depression results from a central deficiency of monoamine function. Most of the early antidepressants worked by affecting several different neurotransmitter chemicals at the same time, but scientists began to work on drugs that would target one specifi c neurotransmitter, while leaving others unaffected (Table 1).

Table 1: Antidepressant Medication Classes

Class	Drugs	Class	Drugs
Tricyclic antidepressants (nonselective NE and/or 5-HT inhibitors reuptake inhibitor)	Imipramine Amitriptyline Nortriptyline Clomipramine Desipramine Amoxapine Doxepine Protriptyline Trimipramine	Selective serotonin-reuptake Aminoketone (NE and DA uptake inhibitor) Phenethylamine (5-HT, NE, and DA uptake inhibitor) Other (5-HT re-uptake inhibitor and antagonist)	Fluoxetine Fluvoxamine Paroxetine Sertraline Citalopram Bupropion Venlafaxine Nefazodone Trazodone
Tetracyclic antidepressants	Maprotiline (presynaptic NE re-uptake inhibitor)		Mirtazapine (plus a2-antagonist)
Monoamine oxidase (MAO) inhibitors	Phenelzine tranylcypromine	Selective norepinephrine re-uptake Inhibitor	Reboxetine

DA= dopamine; 5-HT= serotonin; NE=norepinephrine

In the early 1970s, evidence of the role of serotonin (5-hydroxytryptamine or 5-HT) in depression began to emerge and the hypothesis that enhancing 5-HT neurotransmission would be a viable mechanism to mediate antidepressant response was put forward. In 1968, had already found that, when an electrical impulse passed from one neuron to another, serotonin was released into the space between the neurons-the synapse- to help the " message " to be transmitted and its re-uptake, inhibited, which, in clinical terms resulted in helping the patient to recover from depression [10]. The first selective serotonin re-uptake inhibitor was zimelidine developed by Carlsson, but rapidly withdrawn due to its adverse effects. At the same time, in the 1970s, at Eli Lilly, also looking for an antidepressant that could emerge from a molecular design close to the 3-phenoxy-3-phenylpropylamine, but the result was only a compound that was active on norepinephrine re-uptake: nisoxetine. In further research, Wong re-tested other molecules showed a compound later named fluoxetine to be the most potent and selective inhibitor of serotonin reuptake of the series. In fact, fluoxetine was the third specific serotonin re-uptake inhibitor (SSRI) on the market. The first had been fluvoxamine (1983). Fluoxetine appearance in Europe in 1986 just before the United States in December 1987, 294 the term "SSRI" being specially coined for it. Fluoxetine provided rapid relief from the symptoms of depression, without any of the unpleasant side effects associated with the "older" tricyclic antidepressants (dry mouth, constipation, blurred vision, sweating, and weight gain) or the dietary restrictions that were necessary with MAOI drugs. By 1994, it was the number two bestselling drug in the world [11].

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