Treating Depression in Adults

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Depressive Disorders represent a broad and heterogeneous group of commonly diagnosed psychological disorders. The DSM adequately describes the symptoms of depression and differentiates well between many depressive diagnoses. Psychologists are well-trained in psychological treatments of depression. This article is designed to increase your knowledge of pharmacological treatments of depression.

Because we see patients much more frequently and for a greater amount of time, it is important to understand the medications they are using. The neurochemical basis for medication selection is an important part of an overall understanding of your patient and their medication.

Monoamine Hypothesis of Depression

There are three primary monoamines (neurotransmitters) thought to be involved in depression: norepinephrine (NE), serotonin (5HT) and dopamine (DA). The classic "monoamine hypothesis" states that depression results from a deficiency and/or malfunctioning of one or more of these monoamines. Virtually all traditional antidepressant medications target one or more of these monoamines.

There are three present hypotheses of malfunctioning monoamines. The first involves excessive reuptake. The effect of this abnormality is that significant amounts of monoamines, already released from the presynaptic cell, are rapidly reabsorbed into the neuron. This reabsorption/reuptake leads to decrease volume of the monoamine in the synapse.

The second hypothesized malfunction involves an initial decrease of monoamines into the synapse. This may be due to a reduction in the synthesis of the monoamine or an inability to adequately store monoamines in vesicles.

The third hypothesis involves monoamine oxidase (MAO). In this hypothesis MAO becomes too active and causes an excessive degradation of monoamines; thereby decreasing total volume of monoamines.

Neurotropic Hypothesis of Depression

Virtually all antidepressants have an effect on the monoamine neurotransmitter systems.

However, although antidepressants have an immediate effect on monoamines, they do not have an immediate effect on symptoms and levels of depression. This has led to the hypothesis that the immediate rise in monoamines that occurs with antidepressant treatment leads to an eventual downstream change in protein synthesis. It is possible that this rise in protein synthesis is significant in the treatment of depression. The findings are inconsistent but there is often an increase in protein synthesis occurring concurrent with antidepressant treatment.

One particular protein related to monoamine functioning is Brain Derived Neurotropic Factor (BDNF). BDNF is important to the growth and development of immature neurons; it enhances the survival and function of adult neurons, and maintains synaptic function.

Decreased levels of BDNF may cause neuronal atrophy or loss. Increased levels of BDNF are thought to be involved in neurogenesis and synaptic plasticity.

Brain imaging studies have indicated that depressed patients have decreased volume in hippocampus and prefrontal cortex. Furthermore, BDNF in those areas has been shown to be low in depressed patients. Additionally, there appears to be a correlation between the levels of BDNF and the severity of the depression.

Typical antidepressant medications are believed to have an effect on BDNF. Additionally, and very important for psychologist who don't presently prescribe, there are two non-pharmacological treatments that directly affect levels of BDNF: ECT and **exercise**. **A depressed patient can significantly increase levels of BDNF with as little as 20 minutes of exercise.**

A Quick Reminder of Neuroanatomy and a Little Neurochemistry

Malfunctioning of certain brain regions, manifesting either as hypo or hyperactivity may hypothetically be involved in particular symptoms of depression.

The Prefrontal Cortex is thought to be involved in concentration, interest, mental fatigue, guilt, suicidality, feelings of worthlessness, and mood.

It is hypothesized that the Amygdala is involved with feelings of guilt, suicidality, feelings of worthlessness, and mood.

The Nucleus Accumbens is thought to be primarily involved with pleasure, interests, fatigue, and energy.

Malfunctioning in the Striatum can create problems with physical fatigue.

The Hypothalamus is thought to be the primarily culprit involved in problems with sleep and appetite.

This quick overview of neuroscience is important because there are hypothesized particular circuits involved with different symptoms of depression. An apathetic depression has more involvement from NA and DA than an agitated depression. Agitated depressions are most linked with 5HT.

DA and NE are hypothetically linked with emotional regulation, self-monitoring, goal-setting, priority planning, organization, and apathy. Apathy is a distinct symptom of depression leading to anhedonia, decreased libido, loss of motivation, and physical fatigue.

Inefficient or dysfunctional 5HT has been hypothetically linked to feelings of guilt and worthlessness, problems with weight and appetite, and suicidal ideation.

In selecting particular antidepressant medications, it is important to know something about particular symptoms and the malfunctioning monoamines linked to the symptoms.

Classes of Antidepressants

Monoamine Oxidase Inhibitors: These are an effective class of antidepressant medication. However, they pose the greatest risk in terms of potential medical side effects and therefore, are generally reserved for treatment resistant (or refractory) depressions.

They are associated with risks of hypertensive crisis and serious drug interactions with other antidepressants, decongestants, ephedrine, pseudoepherine, amphetamines, appetite suppressants, and opiate derivatives. The hypertensive crisis associated with MAOIs also occurs with the ingestion of tyramine. Foods containing tyramine are aged cheeses, red wines, tap beers, fava beans, sauerkraut, soy sauce, tofu, other soy condiments, and dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry and fish.

Although reserved for refractory depressions, the patient must be free of suicidal ideation, impulsivity, irritability, and cognitive impairment.

Of all the MAOIs, the selegiline patch (Emsam) provides the highest level of safety. Because it bypasses the gastrointestinal tract, the problems with diet that lead to hypertensive crisis are drastically reduced. You will also find that two other MAOIs, phenelzine (Nardil) and tranylcypromine(Parnate)are commonly used for refractory depressions.

Tricyclic Antidepressants: TCAs are also effective for treatment resistant or refractory depression, particularly when melancholia is a prominent symptom. Of the tricyclics, nortriptyline (Pamelor) is thought to be the best tolerated.

Common Side Effects of TCAs:

- *Anticholinergic*: dry mouth, dry skin, blurred vision, constipation, paralytic ileus, cessation of intestinal movement, urinary retention.
- *Andrenergic*: sweating, sexual dysfunction, orthostatic hypotension
- *Antihistiminic*: sedation, weight gain.
- *Other*: lowered seizure threshold, cardiac arrhythmia, agranulocytosis, sweating, rashes, anxiety, elevated heart rate.

TCAs are quite toxic and even a small overdose can be lethal. They should not be used with suicidal patients.

Reuptake Inhibitors: Reuptake inhibitors are divided into classes according to the targeted neurotransmitter (monoamine).

Serotonin Reuptake Inhibitors

- *Celexa (citalopram):* Advantages: Minimal interaction with other drugs; Minimal sedation and weight gain; better tolerated than most antidepressants. Disadvantages: May initially cause anxiety.
- *Lexapro (escitalopram):* Advantages: Minimal interaction with other medications; Minimal sedation and weight gain; better tolerated than most antidepressants. Disadvantages: May initially cause anxiety.
- *Prozac (fluoxetine):* Advantages: Activating, long half life. Disadvantages: Long half life; activating; more interaction with other medications.
- *Luvox (fluvoxamine):* Advantages: Helpful for OCD; helpful for anxious depressions or comorbid anxiety disorders; helpful for delusional or psychotic depressions.
- *Paxil (paroxetine):* Advantages: Beneficial as an anxiolytic; preferred treatment for anxious depression. Disadvantages: Weight gain; cannot be used during pregnancy; discontinuation symptoms, interactions with other medications.
- *Zoloft (sertraline):* Advantages: Good balance of activation. Disadvantages: More gastrointestinal side effects than other SSRIs. Note: may also affect DA.

Serotonin and Norepinephrine Reuptake Inhibitors

- *Pristiq (Desvenlafaxine):* Advantages: Used for depression with fibromyalgia.
- *Cymbalta (duloxetine):* Advantages: Good for severe depression; may be useful for pain and cognition problems of fibromyalgia. Disadvantages: May cause nausea and sedation; may cause hypertension; use with caution in presence of cardiac impairment.
- *Effexor (venlafaxine):* Advantages: Good for severe depression, GAD, social anxiety, and possibly chronic pain. Disadvantages: May cause hypertension; Increased gastrointestinal side effects.
- *milnacipran*: Advantages: Energizing and activating; useful for pain and cognitive problems associated with fibromyalgia. Disadvantages: sweating and urinary hesitancy; use with caution in cardiac patients; not yet approved in USA.

Norepinephrine Reuptake Inhibitors

- Strattera (atomoxetine): Advantages: Good for cognitive symptoms of depression but not approved as an antidepressant; minimal sexual side effects. Disadvantages: May cause sedation or anxiety; can increase heart rate and blood pressure.

Serotonin Antagonist and Reuptake Inhibitors

- Deseryl (*trazodone*): Advantages: Sedation; lacks sexual side effects of SSRIs. Disadvantages: sedation; may block hypotensive effects of some antihypertensive medications.
- *Serzone (nefazadone*): Advantages: Affects multiple neurotransmitters. Disadvantages: Common side effects are nausea, headache, anxiety, sedation, dizziness; rarely used because of potential liver problems.

Atypical –*These are not reuptake inhibitors but have a similar action*

- *Remeron (mirtazapine):* Advantages: Good for severe depression and insomnia; less sexual dysfunction. Disadvantages: Significant weight gain and sedation; use with caution in cardiac, renal, and hepatic patients.
- *Wellbutrin (buproprion)*: Advantages: Some stimulant effect; ameliorates the sexual side effects of SSRIs; useful in treating nicotine addiction; also effects DA thus proving help for patients who experience reduced positive affect; may improve cognitive slowing; reduces hypersomnia and fatigue. Disadvantages: Can cause anxiety and insomnia; can lower seizure threshold for eating disordered patients; use with caution in cardiac patients.
- *Buspar (buspirone)*: Advantages: Used mainly in treatment of anxiety and is highly effective for anxiety. Disadvantages: Isn't quickly effective, in fact, full effect isn't felt for many weeks; can cause nausea, headache, dizziness, and paradoxical anxiety.

Common side effects of Reuptake Inhibitors: Sexual dysfunction, weight gain (slow and usually only with long-term use), mid-nocturnal awakening, gastro-intestinal distress.

The following medical conditions may have an effect on depression:

Addison's disease
AIDS
Anemia
Asthma
Chronic Fatigue Syndrome
Chronic Infection
Chronic Pain
Congestive Heart Failure
Cushing's disease
Diabetes
Hypothyroidism
Hepatitis
Influenza
Lyme disease
Cancer
Malnutrition
Multiple Sclerosis
Parkinson's disease
Premenstrual dysphoria
Prophyria
Rheumatoid Arthritis
Sleep Apnea
Systemic Lupus
Ulcerative Colitis
Uremia

The following medications and substances can cause depression:

Alcohol
Antianxiety medications
Antihypertensives
Antiparkinsonian drugs
Birth control pills
Cortocosteroids and other hormones

Serotonin Syndrome:

Elevated serotonin levels (usually occurring with changes in medications or inappropriate medication combinations) can be problematic. Every psychologist should be aware of the symptoms of serotonin

syndrome. Symptoms include: agitation or restlessness, diarrhea, increase in heart rate, hallucinations, increased body temperature, loss of coordination, nausea, overactive reflexes, rapid changes in blood pressure, and vomiting. The combinations of MAOIs, Triptans (common migraine medications) and some opioid derivatives with serotonergic agents are particularly problematic.

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