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REVIEW ARTICLE

Depression: Psychiatrist is a Best Prescriber for an Antidepressant Medication

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ABSTRACT
Depression is a medical illness that involves the brain. Antidepressants are only one kind of medicine used to treat depression. Depression is a serious but treatable problem that should not be ignored. Many people require some form of treatment by a doctor or other health care professional for their depression. This review will tell us the what research found about the possible benefits and side effects of antidepressants. This article reviews the" me too " antidepressants drugs which block & inhibit the reuptake of different type of neurotransmitter like serotonin (SE) and norepinephrine (NE). According to Research & health care experts patient should best to get antidepressants medication from a psychiatrist who is well trained and up-to-date on the use of psychoactive drugs. Monitoring of antidepressant drugs enables us to individualise drug doses based on rational therapy, minimalise side effects, reduce morbidity and mortality and cut the cost of health care. Proper dosage can be critical, and the choice of effective drugs can complete cure the depression.
KEY WORDS : *Therapeutic Drug Monitoring (TDM), Antidepressent Drug , Tri cyclic Antidepressent , Levomilnacipran (Fetzima) , SSRI*

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INTRODUCTION

Fiscal constraints in the health care system have led to closer scrutiny of medications with mechanisms of action similar to those of standard reference drugs. Often referred to informally as "me too" medications, these drugs may have similar efficacy to reference drugs but different adverse effects or drug interactions. Such differences may result in a preference for one agent over another in particular situations. Otherwise, the decision about which agent to use is most often based on price or the prescriber's familiarity with a product.[1-3] . Antidepressants were developed in the 1950s, and their mechanism of action is thought to be by increasing the levels of extracellular synaptic neurotransmitters such as serotonin, noradrenaline, and dopamine. The original antidepressants were known as tricyclics because of their chemical structure. Since the 1980s a new generation of antidepressants has been developed and marketed based on their mode of action [4]. According to clinical psychology, depression is a syndrome, a cluster of emotional, physical, and behavioral symptoms characterized by sadness, low self esteem, loss of pleasure, and, sometimes, difficulty functioning [5]. Major depression, is one of the most prevalent mental disorders in present life .Antidepressants are prescribed mainly for people with depression, although some are also used for anxiety disorders and other conditions, including chronic pain and enuresis. They are one of the most commonly prescribed medications [6].The dramatic rise in consumption of antidepressants in developed countries in the past two decades has been mainly due to increase in the use of selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors and other new generation antidepressants which are now the most commonly prescribed antidepressants in the world. In clinical practice, optimum individual doses are often guided by trial-and-error[7].

There are several commonly used classes of antidepressants. These include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibiors (SNRIs), atypical antidepressants (eg, bupropion and mirtazapin), and serotonin antagonists and reuptake inhibitors (SARIs). Older classes of antidepressants (tricyclic antidepressants - TCAs and monoamine oxidase inhibitors - MAOIs) are still used occasionally. Therapeutic drug monitoring (TDM) in the field of psychotropic drugs began with the

tricyclic antidepressants in the 1960s . Although there is sufficient evidence for the benefits of TDM in optimizing antidepressant therapy, its current use in routine care is far from optimal [8].

These feelings are just one part of everyday life for most people. However, if the feelings are overwhelming or persistent, you may benefit from psychological evaluation and treatment. Depression of this type can be effectively reduced or even eliminated with treatment that is often relatively simple. Professional intervention in serious depression can reduce suffering and improve the quality of life. The most common are **major depression** and **dysthymia.** Major depression can be a harmful, incapacitating, or even dangerous disorder. At its worst, depression can lead to suicide.

CRITERIA FOR DEPRESSION

- Criticizing, attacking, and berating yourself.
- Skipping days of work or not going to work.
- Inability to study or pursue serious intellectual or creative interests.
- Loss of interest in sex.
- Avoiding friends or usual social activities, hobbies, or recreations.
- Inability to enjoy activities or events in which you normally take pleasure.
- Neglecting yourself physically (in terms of grooming and hygiene).
- Forgetfulness.
- Crying a lot or feel like crying without knowing why.
- Feeling irritable and getting into arguments easily.
- Increased and excessive use of alcohol or other recreational drugs.

Dysthymic disorder is an ongoing depression that may not be as severe as a major depressive disorder, but is chronic, often lasting for years and, for some people, as long as they can remember.

CRITERIA FOR DYSTHYMIA

Feeling unhappy or "down" most of the time on most days
AND
While depressed, at least two of the following symptoms are present:
• Poor appetite or overeating
• Difficulty sleeping or sleeping too much
• Low energy or fatigue
• Low self-esteem
• Poor concentration or difficulty making decisions
• Feeling hopeless
• Excessive use of alcohol or other recreational drugs [9].

Antidepressants are usually started at low dosage and then increased. Significant improvement should occur in two to six weeks after taking a therapeutic dose of the drug; do not expect it to work immediately, although some people feel better within a few days. If one antidepressant does not work, another may be effective. Inadequate dosage or inadequate length of time on the drug is the most common cause of treatment failure. Antidepressant medications are usually taken for four to six months. If depression recurs when the medication is stopped, these antidepressants may be taken on an indefinite basis [10].

POSSIBLE TREATMENTS FOR DEPRESSION

Depression is treated with medicines, talk therapy (where a person talks with a trained professional about his or her thoughts and feelings; sometimes called “psychotherapy” or “counseling”), or a combination of the two. This review looks at research only on the medicines used to treat depression called antidepressants. A number of different drugs, referred to as antidepressants, are used to treat depression.

Psychotherapy is helpful in treating depression. Medication with antidepressants is the quickest way to relieve major depression and is helpful for severe depression associated with suicidal thoughts and/or major disruption of functioning. It relieves symptoms and allows you to go on with your life. In general, two thirds of patients with a major depressive disorder will respond positively to the use of medication within two weeks to two months. Most of the rest will get better when they try a different antidepressant. Major depression is one of the most treatable of medical conditions. Medication also works for dysthymia. Although the improvement may look less dramatic than in major depression, it can lead to a meaningful improvement in your life.[11]

The best treatment for both major depression and dysthymia is a combination of medication and talk therapy. Numerous studies show that both psychotherapy and medication are very effective in treating

depression. Depression inhibits your ability to see the world clearly and act effectively. By reducing anxiety and depression, drugs help some people clarify their thinking and become more active [11].

MEDICATIONS ARE USED TO TREAT DEPRESSION

Antidepressants belong to several different categories. They affect the function of certain neurotransmitters in the brain, although the process is not completely understood.

1. Revessible inhibitor of MAO-A (RIMAs) : Moclobemide , Clorgyline
2. Tricyclic Antidepressents (TCAs)
    a) NA + 5-HT reuptake inhibitors : Imiramine , Amitriptyline* , Trimipramine, Doxepine , Dothiepin , Clomipramine
    b) Predominantly NA reuptake inhibitors : Desipramine , Nortriptyline , Amoxapine , Reboxetine
3. Selective Serotonin reuptake inhibitor (SSRIs) : Fluoxetine* , Fluvoxamine , Paroxetine , Sertraline , Citalopram , Escitalopram
4. Atypical Antidepressent : Trazodone , Mianserin , Mirtazapine , Venalafaxine ,Duloxetine , Tianeptine , Amineptine , Bupropion
5. New generation Antidepressent drug : Levomilnacipran (Fetzima™)
6. Other antidepressants
    a) Melatonin receptor agonist with 5-HT2C receptor antagonist properties: agomelatine
    b) Serotonin partial agonist: gepirone
    c) Monoamine oxidase inhibitors (non-selective) : Phenelzine, tranylcypromine, isocarboxazid

(Note : Amitriptyline* & Fluoxetine* listed in WHO's list of essential medicines for use in depressive disorders)

The medications that currently are most widely used to treat both major depression and dysthymia belong to categories referred to as SSRIs, "selective serotonin reuptake inhibitors" or SNRIs "seratonin/ noradrenaline reuptake inhibitors. They take their name from the effect they have on a neurotransmitters in the brain known as serotonin and noradrenaline, which are believed to play a role in causing depression [12-15].

1. **Tricyclic Antidepressent :-** With the tricyclic antidepressant drugs, TDM is a long established tool for finding the individual dose optimum. TDM has been reported to increase not only efficacy and safety of TCAs, but also cost-effectiveness in the treatment of depression and is highly recommended for most tricyclic antidepressants. It reduces the risk of intoxication, and for many TCAs, a plasma concentration-clinical effectiveness relationship has been shown. TCAs are also associated with orthostatic hypotension, sedation, and anticholinergic effects (Table 1) and MAOIs commonly cause orthostasis as well [16].
    - Desipramine and Imipramine are two of the most widely prescribed cyclic antidepressants.
    - Among the TCAs, amitriptyline is known to have the highest degree of sedative effect. This compound has frequently been used as reference in studies on newer types of antidepressants [18].
    - Doxepin , Trimipramine , and Amoxopine are antidepressants that are currently not widely used. Basic characteristics of antidepressant drugs shown in (Table 2).

Table 1. Antidepressant Drugs Which Show Anticholinergic And Sedative Effects [9-14]

Antidepressant	Sedative Effect	Anticholinergic Effect
(Tricyclic antidepressants (TCAs))		
Amitriptyline	+++	+++
Imipramine	++	++
Trimipramine	++	++
Doxepine	++	++
Clomipramine	++	+(+)
Desipramine	+	+
Protriptyline	++	(+)
Nortriptyline	+(+)	+
Amoxapine	+	+
Selective serotonin reuptake inhibitors (SSRIs)		
Citalopram	0	(+)
Escitalopram	0	(0)
Fluoxetine	0	(+)
Paroxetine	+	+
Sertraline	0	(+)
Non-selective monoamine oxydase inhibitors (MAOI)		
Phenelzine	+	(+)
Tranylcypromine	+	+

(+ is potency of anticholinergic effect)

TABLE 2. Basic Characteristic of Antidepressant Drugs [22-28]

Drug	Bioavailability (%)	Protein binding (%)	Tmax (hours)	Half-life (hours)	Time to reach steady-state (days)
Bupropion (Hydroxybupropion)	87-100	84	3-5	8-26	8
Fluoxetine (Norfluoxetine)	70	95	6-8	4-6 days	3 months
Fluvoxamine	50	80	3-8	15-20	5-10
Citalopram	80	<80	2-4	33-37	7-14
Duloxetine	32-80	96	6-10	8-17	5
Escitalopram	80	56	3-6	22-32	7-10
Paroxetine	30-60	95	3-5	12-44	4-14
Sertraline	>44	98	4-8	26-36	7
Trazodone	>60	89-95	1-4	distribution 3-6 ,elimination 5-9	2-3
Venlafaxine (O-desmethylvenlafaxine)	40-45	27	1-6	5	3

- Tmax – time to reach maximum plasma concentration

2. **Selective Serotonin Reuptake Inhibitor (SSRIs):-**Serotonin (5-hydroxytryptamine) is an ancient chemical, it is present in fungi, plants, and animals. It belongs to a class of biochemicals called monoamines, which also includes noradrenaline and dopamine. Many adaptive processes evolved to be regulated by serotonin, including cell differentiation, temperature, platelet activation and the clotting process, digestion and gut movement, insulin, electrolyte balance, neuronal apoptosis, cerebral blood flow, emotion, attention, aggression, mood, reproductive function, and mating behavior. Because serotonin regulates many adaptive processes, antidepressants based on serotonin reuptake inhibition could have many adverse health effects [29].

   The SSRIs are the first-line and the most commonly prescribed antidepressants. All SSRIs share similar pharmacologic actions, including minimal anticholinergic, antihistaminic, and α 1-adrenergic blocking effects, and potent presynaptic inhibition of serotonin reuptake [30].

   The SSRIs are all lipophilic agents, which are well absorbed via the gut mucosa. Fluoxetine, paroxetine, and especially sertraline are highly bound to plasma proteins (95-98%), whereas the protein binding is less pronounced for citalopram and fluvoxamine (≤80%).All of the SSRIs are predominantly eliminated by cytochrome P450 catalyzed oxidation in the liver. Hence, higher doses of these drugs produce a disproportionate increase in their plasma concentrations. The SSRI drugs are also used to treat a number of other psychiatric problems including panic disorder, social phobia, and obsessive-compulsive disorder [31]. An additional drug that is widely used to treat both major depression and dysthymia is bupropion. For reasons that are not understood, some people respond to one drug and do not respond to another drug in the same class. Additionally, the severity of side effects of each drug varies from person to person. Therefore, if you do not get better after a therapeutic trial of one drug or have unacceptable side effects, you are still likely to respond well to another antidepressant. Occasionally people respond best to a combination of medications and may, paradoxically, have fewer side effects. These antidepressants are generally the first choice for treating both dysthymia and major depression. They are as effective as the older drugs used to treat depression and have fewer and less serious potential side effects[32].

Side effects of SSRI's

Sexual side effects **:** The most common side effect of fluoxetine **,** sertraline **,** paroxetine **,** citalopram **,** venlaxafine**,** and fluoxamine is sexual dysfunction. People are highly variable in how they respond to these sexual side effects. The next most common is decreased libido, or sexual desire.

Insomnia and agitation **:** All SSRIs and SNRIs and bupropion (especially) may cause mild to moderate insomnia or restlessness, agitation and nervousness.

Sedation **:** All of these medications occasionally cause sleepiness in some people. With mirtazapine this is a frequent problem.

Weight gain and loss **:** All SSRIs and SNRIs may cause weight gain in some people; this has been frequently observed in clinical practice, though research data are limited. This appears to be most frequent with mirtazapine and least common with escitalopram oxalate . At the same time, fluoxetine**,** sertraline , paroxetine , fluoxamine **,** and bupropion may cause temporary loss of appetite and consequent weight loss when they are started.

Anticholinergic side effects **:** All SSRIs may cause anticholinergic side effects (dry mouth, constipation, difficulty urinating) and orthostatic hypotension (low blood pressure) [34-36].

Monoamine oxidase inhibitors (MAOIs)

The older non-selective Monoamine Oxidase Inhibitors (MAOIs) inhibit both Monoamine Oxidase A and B irreversibly .MAOIs are antidepressants generally used for patients who have not responded to other antidepressant drugs. They are not usually the first choice but can be very effective and seem to work well in certain patients who are considered to have atypical depressions (depression with overeating and too much sleeping). The following MAOIs have comparable effectiveness and similar side effects [37].

- Tranylcypromine
- Phenelzine
- Isocarboxazid

MAOIs have significant side effects. They provoke dangerously high blood pressure when combined with a substance known as tyramine, which is contained in some food, beverages, and drugs.

ATYPICAL ANTIDEPRESSANT

Antidepressants that affect predominantly 2 neurotransmitter systems, such as duloxetine and venlafaxine, are referred to as dual-acting agents. Dual-acting drugs that block the reuptake of SE and NE are commonly referred to as serotonin norepinephrine reuptake inhibitors (SNRIs). Tricyclic antidepressants (TCAs), in particular the secondary amines, affect both the SE and NE systems, but they also interact with a variety of other receptors, which predisposes them to cause more adverse effects than agents with greater selectivity. Other dual-acting antidepressants include bupropion, which inhibits the reuptake of NE and dopamine into presynaptic neurons, and mirtazapine, which influences NE and SE transmission via mechanisms different from that of the SNRIs. In addition to duloxetine and venlafaxine, there are two other SNRI-like dual-acting antidepressants, namely milnacipran and sibutramine.

Duloxetine and venlafaxine are SE and NE reuptake pump inhibitors with different affinities for the SE and NE receptor . Relative to venlafaxine, duloxetine has 106 times greater potency at the human SE transporter and 331 times greater potency at the human NE transporter. Therefore, the differential affinity (favouring SE over NE transporters) of venlafaxine is considerably higher than that of duloxetine in (Table 4). Given this preferential affinity of venlafaxine, lower therapeutic doses would result in predominantly serotonergic activity, similar to that of a selective serotonin reuptake inhibitor (SSRI) [38-40].

Duloxetine

Duloxetine is acid-labile and is therefore formulated with an enteric coating that begins to dissolve at pH 5.5. Administration of duloxetine with food delays absorption by 2 hours and decreases the area under the curve (AUC) for concentration vs time by 10%. If this drug is taken in the evening rather than in the morning, absorption is delayed by about 3 hours and clearance is increased by about 33%. Duloxetine is metabolized by cytochrome P450 enzymes (specifically CYP2D6 and CYP1A2) to numerous metabolites **(Table 3).** Duloxetine is a moderate inhibitor of CYP2D6 but only a weak inhibitor of CYP1A2 in vivo.Most (70%) of the metabolites of this drug are excreted in the urine, with about 20% being excreted in the feces. The elimination half-life averages 12 hours (range 8–17 hours) [41-42].

Venlafaxine

Venlafaxine is rapidly absorbed after oral administration and is unlike duloxetine in that administration with meals does not significantly delay absorption. Venlafaxine is widely distributed throughout the tissues, and has much lower protein binding in plasma than duloxetine (27% vs 96%). Duloxetine and venlafaxine have similar pharmacologic profiles and similar efficacy in the treatment of depression. However, their pharmacokinetic and adverse effect profiles differ [48-50].

NEW GENERATION ANTIDEPRESSANT DRUG

Levomilnacipran (Fetzima™): The U.S. Food and Drug Administration (FDA) has approved Fetzima. Fetzima (levomilnacipran) is an extended release selective norepinephrine and serotonin reuptake inhibitor is indicated for the treatment of major depressive disorder (MDD). The chemical name of levomilnacipran is (1S,2R)-2- (aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride; its empirical formula is $C_{15}H_{23}ClN_2O$ and its molecular weight is 282.8 g/mol. Levomilnacipran (Initial US approval 2013) is the 1S,2R-enantiomer of milnacipran. The dose of FETZIMA should not exceed 80 mg once daily when used with strong CYP3A4 inhibitors [51-54].

Fetzima may cause serious side effects, including :

1. High blood pressure (hypertension)
2. Increased heart rate (palpitations)
3. Abnormal bleeding or bruising
4. Glaucoma (increased eye pressure)
5. Urinary hesitation and retention (difficulty urinating or unable to urinate)

6. Hypomania (manic episodes).
   Symptoms of manic episodes include: greatly increased energy , severe problems sleeping , racing thoughts , reckless behavior , unusually grand ideas , excessive happiness or irritability , talking more or faster than usual.
7. Discontinuation symptoms suddenly Stopping Fetzima may cause serious symptoms like : anxiety , irritability , high or low mood ,feeling restless or sleepy, headache , sweating , nausea , dizziness , electric shock-like sensations , tremor , confusion ect.
8. Low levels of salt (sodium) in your blood **:-** Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet.
   if you take the following medicines than tell your health care provider about it, like
   - medicines used to treat migraine headache (triptans)
   - tramadol
   - diuretics
   - over-the-counter supplements such as tryptophan or St. John's Wort
   - medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, fentanyl, tryptophan, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors(SNRIs), buspirone, or antipsychotics
   - sibutramine
   - nonsteroidal anti-inflammatory drugs (NSAIDS)
   - warfarin[55]

TABLE 3. Cytochrome P450 (CYP) Forms Involved In The Metabolism Of Antidepressant Drugs [33,36,41,18]

Drug	CYP	Active metabolite
Bupropion	2B6	hydroxybupropion, threohydrobupropion, erythrohydrobupropion
Citalopram	2C19, 3A4, 2D6	desmethylcitalopram, didesmethylcitalopram, citalopram-N- oxid
Duloxetine	1A2, 2D6	None
Escitalopram	2C19, 2D6, 3A4	desmethylcitalopram, didesmethylcitalopram
Fluoxetine	2D6, 2C9, 2C19, 3A4, 2B6	Norfluoxetine
Fluvoxamine	1A2, 2D6	fluvoxamine acid
Mirtazapine	3A4, 2D6, 1A2, 2B6	Desmethylmirtazapine
Paroxetine	2D6, 3A4, 1A2, 2C19, 3A5	None
Sertraline	2B6, 2C19, 3A4, 2D6, 2C9	Desmethylsertraline
Trazodone	3A4, 2D6	m-chlorophenylpiperazine
Venlafaxine	2D6, 3A4, 2C19	O-desmethylvenlafaxine, N-desmethylvenlafaxine

TABLE 4 : Pharmacokinetic Summary of Duloxetine and Venlafaxine

Pharmacokinetic parameter	**Venlafaxine**	**Duloxetine**
Absorption (%)	≥92	91
Bioavailability (%)	45	50
Plasma protein binding (%)	30	96
Volume of distribution	7.5 L/kg (parent compound), 5.8 L/kg (metabolite)	1640 L
Metabolism	Extensive hepatic (CYP2D6)	Extensive hepatic (CYP2D6, CYP1A2)
Active metabolites	O-Desmethylvenlafaxine(ODV)	5-hydroxy-duloxetine,6-methoxy-duloxetine
Clearance	1.21 L h–1 kg–1 (parent compound), 0.4 L h–1 kg–1 (ODV)	101 L/h
Elimination half-life (h)	5 (parent compound), 11 (ODV)	About 12 (range 8–17)
Steady state (days)	3 (parent compound, ODV)	About 3

- CYP = cytochrome P450, O-desmethylvenlafaxine (ODV)

CONCLUSION

Monitoring of antidepressant drugs enables us to individualise drug doses based on rational therapy, minimalise side effects, reduce morbidity and mortality and cut the cost of health care. According to Research Scientist & health care experts patient should best to get antidepressants medication from a psychiatrist. If this is not possible, your regular physician can prescribe antidepressants. Effective medication depends on correct diagnosis. Diagnosis of psychological symptoms requires specialized

training and prescribing psychoactive drugs optimally requires experience. Proper dosage can be critical, and the choice of effective drugs can be subtle**.** Therefore, a psychiatrist is the best physician to prescribe antidepressants. It is important to see a psychiatrist who is well trained and up-to-date on the use of psychoactive drugs. Psychopharmacologists are more likely to choose the most suitable drug for patient and are more likely to prescribe appropriate doses. They are trained to have an organized strategy for trying different drugs if the first is not successful.

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