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A review on Newer Antidepressant Drugs

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Abstract-

Antidepressant drugs are the drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other and many of them have other associated properties. Particularly over the past two decades, a large number of antidepressants with an assortment of effects on reuptake / metabolism of biogenic amines. On pre or post junction aminergic / cholinergic receptors have became available so that a cogent classification is difficult. On pre or post functional aminergic/ cholinergic receptors have became available so that a cogent classification is difficult. Most clinically useful antidepressant drugs potentiate, either directly or indirectly the actions of norepinephrine and serotonin in the brain. Mania is caused by an overproduction of these neurotransmitters. The potency of antidepressant drugs in blocking neurotransmitter uptake often does not correlate with clinically observed antidepressant effects.

Keywords- Tricylic antidepressant drugs, selectively serotonin reuptake inhibitors, Monoaminooxidase inhibitors, serotonin.

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Introduction-

Classification of Antidepressant Drugs:

- Reversible inhibitors of MAO-O(RIMAs)
  Moclobemide
- Tricyclic antidepressants(TCAs)
  NA+5HT reuptake inhibitors: Imipramine
  Predominantly NA reuptake inhibitors: Desipramine
- Selectively serotonin reuptake inhibitors(SSRIs)
  Fluoxetine
- Atypical antidepressants
  Trazodone

Table-1. Shortcomings of Antidepressant Drugs

Name	Group	Side effects
Amitriptyline	Tricyclic Antidepressants (TCAs)	Blurred vision bowel problems, coma concentration problems, confusion.
Amoxapine	Tricyclic Antidepressants (TCAs)	Decrease in urine volume difficulty in breathing, difficulty in passing urine, difficulty in speaking.
Bupropion Hydrochloride	Selectively serotonin reuptake inhibitors (SSRIs)	Anxiety, dry mouth, hyperventilation, irregular heartbeats, irritability, shortness of breath.
Citalopram	Selectively serotonin reuptake inhibitors (SSRIs)	Very serious allergic reaction to this drug is rare. However, get medical help right away if any symptoms of a serious allergic reaction noticed.

Clomipramine	Tricyclic Antidepressants (TCAs)	Tiredness and blurred vision may occur. Anxiety symptoms may temporarily worsen when you first start taking clomipramine.
Dosulepin	Tricyclic Antidepressants (TCAs)	Dry mouth. Drowsiness. Blurred vision. Constipation. Nausea. Difficulty in passing urine. Sweating.

Limitation of Antidepressants-

In short-term clinical trials, response is operationally defined as a 50% reduction from baseline scores on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). While response to therapy is a useful endpoint in short-term clinical trials, the endpoint in long-term trials and the goal of treatment in clinical practice should be remission.[6] Response rates of all antidepressants are reportedly 60% to 70%, leaving a sizable minority, 30% to 40%, who do not respond to the drug treatment or will have only a partial response.

Currently available antidepressants work on the monoamine-based mechanism of action and enhance either singly, or in combination, serotonergic, noradrenergic, and, to a lesser extent, dopaminergic neurotransmission. TCAs have heterogeneous effects on neurotransmitter systems. Some TCAs, such as imipramine, clomipramine, and amitriptyline, have a dual mechanism of action, with roughly equivalent selectivity for norepinephrine and serotonin. Conversely, TCAs, including maprotiline, desipramine, and nortriptyline, are substantially more selective for norepinephrine then they are for serotonin.

SSRIs principally inhibit serotonin while newer agents, such as venlafaxine, mirtazapine, duloxetine, and milnacipran, enhance both serotonergic and noradrenergic neurotransmission. Traditionally, drugs that had multiple mechanisms were synonymous with “dirty drugs” because it implied unwanted side effects. We typically think of TCAs in this regard. Later, there was a trend to develop more selective drugs, such as the SSRIs, which attempted to remove unwanted side effects. More recently, there has again been a trend to add multiple mechanisms together to improve both tolerability and efficacy. Evidence for enhanced efficacy among antidepressants with dual action versus single action has been examined in a number of studies and meta-analyses.

Delayed Onset of Action-

Although the synaptic effects of antidepressants occur within hours of ingestion, the therapeutic or clinical effects are not seen for several weeks. In controlled trials, statistically significant differences between active treatment and placebo often require 4 weeks or more to emerge. The usually expected delay of efficacy for any antidepressant is between 10 days and 3 weeks at therapeutic doses. There are a number of potential consequences of delayed onset of antidepressant action. These may include increased vulnerability for suicide, longer hospital stays, prolonged physical, psychological, and social impairment, as well as the increasing economic burden of depression.

Clinical trials to date have not been designed to adequately assess the timing of antidepressant action onset. Primarily, this results from no set standard for measuring rapid onset of action. A consensus meeting of the European College of Neuro psychopharmacology in 1994 considered that relative responses in the first 2 weeks should form the basis of the claim for rapid-response antidepressant.

In comparison trials with other antidepressants, citalopram has exhibited evidence suggesting a faster time to onset compared with fluoxetine, sertraline, imipramine, and mianserin. In each of the studies, citalopram-treated patients were significantly more improved at week 2 than comparison patients.

Depression requires months or even years of maintenance pharmacotherapy. Some surveys have shown that up to 30% of patients may Co-prescribed an antidepressant that interacts with cytochrome P_{450} (CYP) enzymes and other prescribed medications. It is quite likely that most patients receiving antidepressant medications will take at least one other drug at some point during treatment. In addition, polypharmacy is common in patients with chronic medical conditions. Hence, the physician must constantly be aware and keep up-to-date with potentially clinically significant drug interactions that may occur with the use of antidepressants. Drug interactions are commonly classified as pharmacodynamic or pharmacokinetic. A pharmacodynamic drug interaction occurs when the pharmacologic response to one drug is modified by another drug without the effects being the result of the change in drug concentration. The pharmacokinetic interactions include alternate distortion, distribution, metabolism, or excretion and can result in changing the drug concentration in tissues. However, the majority of drug interactions of concern involve alterations of drug metabolism. The liver is a primary agent of elimination of psychoactive drugs including antidepressants. The most important enzymes in terms of understanding pharmacokinetic drug interactions are those of the CYP system. A complete discussion of drug interactions is beyond the scope of this article; an extensive guide to psychotropic drug interactions is presented by DeVane and colleagues. Briefly, the substrate is an agent or a drug to which metabolism is catalyzed by CYP isozymes. An inducer is an agent or drug that increases the

catalytic activity of the enzyme, allowing for increased rate of metabolism, whereas an inhibitor decreases the catalytic activity of an enzyme, resulting in the opposite effect on the enzyme. Prediction of metabolic drug interactions for the practicing clinician is aided by knowing the metabolic pathways of the drug and whether the drug to be combined in therapy has inhibitory effects on that enzyme. It should be remembered however, that concentration changes do not necessarily translate into clinically meaningful interactions. Table 3 lists the inhibitory potentials of currently available antidepressants. Antidepressants presently may cause significant drug-drug interactions based on their inhibitory potential and the co-prescribed medications. Some of these potential interactions may be serious. Among serotonergic agents, side effects resulting from 5-HT_{2A} may include insomnia, anxiety/agitation, and sexual dysfunction, 5-HT_{2C} may cause irritability and decreased appetite, and 5-HT_3 may cause nausea, vomiting, and headache. Side effects such as tachycardia, blood pressure effects, dry mouth, and sweating, which are associated with newer agents, may also result from noradrenergic receptor stimulation. Side effects of dry mouth, sedation, postural hypotension, may result from interactions at other receptors including muscarinic, cholinergic, histaminergic, and postsynaptic α_1-adrenergic. Thus far, monoamine models of antidepressant action have been the focus of research. Currently, all antidepressants available are hypothesized to work by directly or indirectly enhancing one or a combination of the monoamines, including serotonin, norepinephrine, and dopamine. Increasing amount of accumulated knowledge of the neurophysiologic mechanisms of mood disorders, more treatments will become available in foreseeable future. There are numerous agents currently being developed in the area of mood disorders treatment, including those with novel mechanisms of action. Thus far, monoamine models of antidepressant action have been the focus of research. Currently, all antidepressants available are hypothesized to work by directly or indirectly enhancing one or a combination of the monoamines, including serotonin, norepinephrine, and dopamine. However, monoamine-based hypotheses of antidepressant action are ultimately incomplete as they do not fully explain several important clinical limitations of current treatment including incomplete efficacy, low remission rates, and delayed response. Although the majority of current agents in development largely center on manipulating the monoamine model of antidepressant action, there is a number of new models of antidepressant action for which agents are being developed and studied. The following section will briefly review some new agents in the later stages of clinical development and will comment on some potential novel mechanisms of antidepressant action. Many drugs, including antidepressants, are chiral compounds. A chiral compound is a mixture of two mirror-image stereoisomers of each other, each called an enantiomer; the mixture is called the racemate. It is now well established that a stereospecific biotransformation of a chiral drug can affect its clinical properties. The potential benefits of developing enantiomeric drugs include improvements in

clinical efficacy, enhanced tolerability, refined pharmacokinetic and pharmacodynamic properties, decreased risk for drug interactions, reduced toxicity, improved dosing schedules, and hopefully cost effectiveness.[31] Chiral antidepressants that exist as racemic mixtures are increasingly being relaunched with the inactive isomer removed. For example, citalopram is a racemic antidepressant of R- and S-enantiomers. Escitalopram (S-citalopram) is the first enantiomeric refinement of a racemic antidepressant to be available in clinical practice. Current information suggests that it has advantages of dose reduction, some side effects lessened, and some drug interactions reduced. There is also a suggestion in animal models that it may have the rapid onset of action. As our understanding of stereochemistry improves in relation to psychopharmacology, it is possible that some of the shortcomings of currently available antidepressants may be improved upon through the development of enantiomeric antidepressants. Lanicemine (AZD6765) is an NMDA antagonist developed by AstraZeneca, which is being studied for the treatment of major depression.It was originally developed as a neuroprotective agent, but was redeveloped as an antidepressant following the observation that the anesthetic drug ketamine has potent antidepressant effects, but also has hallucinogenic side effects which make it unsuitable for use as an antidepressant in most circumstances. =Lanicemine is a NMDA receptor antagonist which has been found in human trials to have similar rapid-acting antidepressant effects to ketamine, but with little or no psychotomimetic side effects Importantly, in a 3-week, placebo-controlled phase IIB study of patients with moderate-to-severe MDD, repeated administration of lanicemine (100 or 150 mg per infusion) at 3-day intervals provided sustained antidepressant efficacy, without psychotomimetic effects. These data are consistent with the pharmacological separation of efficacy from psychotomimetic side effects observed in preclinical and phase I studies. Lanicemine treatment, especially the 100-mg dosage, also showed efficacy by several secondary measures. For example, the proportion of patients who recorded a clinical global impression of much improved or very much improved was 65% with the 100-mg dosage at weeks 3, 4, and 5 after treatment began, significantly better than the 25%-30% rates at the same time points in the placebo group. Ketamine can reduce depressive symptoms, but it induces side effects including hallucinations. Ketamine is a very complex drug, an anaesthetic with analgesic, stimulant and psychedelic properties, chemically related to phencyclidine (PCP). The potential for lanicemine were shown from a recent clincial trial. The study, published in the journal *Molecular Psychiatry*, involved giving 152 people with moderate to severe depression who had poor responses to other antidepressants lanicemine or a placebo. The subjects were given the medication three times a week for three weeks. According to New Scientist, those who took lanicemine were found to be less depressed than those who took the pacebo.

References-

[1].http://primarypsychiatry.com/antidepressantpsychopharmacology-current-limitations-and-future-dirctions/

[2]. Diagnostic and Statistical Manual of Mental Disorders. 4th ed rev. Washington, DC: American Psychiatric Association; 2000.

[3].Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA.* 1992;267:1478-1483.

[4].Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. *Psychosom Med.* 1999;61:6-17.

[5].http://www.naurex.com/html/glyx13.html

[6].http://www.nature.com/mp/journal/vaop/nurrent/full/mp2013130a.html

[7].nsel TR, Wang PS. The STAR*D trial: revealing the need for better treatments. Psychiatr Serv 2009; 60: 1466–1467. | Article| PubMed | ISI.

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