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A Review on Antidepressant Drug Bupropion

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ABSTRACT

Major depression extremes of affective disorders which refer to a pathological change in the mood state. Major depressive disorder is associated with substantial morbidity, mortality, family burden, and health care costs. Since no single treatment is uniformly effective,2-4 subsequent interventions are often needed. Secondstep treatments include augmenting the first agent with a second or discontinuing the first agent and beginning a second (switching). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial used an equipoise, stratified, randomized design to evaluate the relative efficacy and tolerability of various antidepressant treatments for outpatients with non psychotic major depressive disorder who had a lack of remission or could not tolerate the selective serotonin-reuptake inhibitor (SSRI) citalopram (Celexa, Forest Pharmaceuticals) or subsequent treatments. The mood change may have a psychotic basis with delusional thinking or 0ccur in isolation and induce anxiety. On the other hand, pathological anxiety may lead to depression anxiety and depression are leading psychiatric disorder now.

Antidepressant these are drugs which can elevate mood in depressive illness. Practically all antidepressant affect monomaniergic transmission in the brain in one way or the other, of them have associated properties. It is typically a third- or fourth-line agent. It has a unique pharmacology, inhibiting the reuptake of noradrenaline Bupropion has been used as an antidepressant for over 20 years, though its licence for such use varies and dopamine, potentially providing pharmacological augmentation to more common antidepressants such as selective serotonergic reuptake inhibitors (SSRIs). This systematic review and meta-analysis identified 51 studies, dividing into four categories: bupropion as a sole antidepressant, bupropion coprescribed with another antidepressant, bupropion in 'other' populations (e.g. bipolar depression, elderly populations) and primary evaluation of side effects.

Keywords: antidepressant; depression; selective serotonin reuptake inhibitors

Introduction

Antidepressants are medications used to treat MDD some anxiety disorders, some chronic pain conditions, and to help manage some addictions. Common side-effects of antidepressants include dry mouth weight gain nausea and emotional blunting. There is a slight increased risk of suicidal thinking and behavior when taken by children, adolescents, and young adults. A discontinuation syndrome can occur after stopping any antidepressant which resembles recurrent depression.

Some reviews of antidepressants for depression in adults find benefit while others do not. Evidence of benefit in children and adolescents is unclear. The twenty-one most commonly prescribed antidepressant medications were found to be more effective than placebo for adults with major depressive disorder in a 2016 meta-study. There is debate in the medical community about how much of the observed effects of antidepressants can be attributed to the placebo effect, with some claiming that there is no effect above and beyond it. Most research on whether antidepressant drugs work is done on people with very severe symptoms, a population who exhibits much weaker placebo

responses, so the results cannot be extrapolated to the general population.

There are effective treatments for depression which do not involve medications or may be used in conjunction with medications.

These drugs 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. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and pre/post- junctional aminergic/ cholinergic receptors have become available so that a cogent classification is difficult.

There are several major classes of antidepressant drugs, the best known of which include the tricyclic antidepressants, monoamine oxidase inhibitors (MAOI) and selective serotonin reuptake inhibitors (SSRIs). Other important groups include the norepinephrine reuptake inhibitors (NRIs),theserotonin-norepinephrine reuptake inhibitors (SNRIs),and the atypical antidepressants, a disparate group of agents that possess unique structural features and mechanisms of action.

Chemically speaking, depression is apparently caused by reduced quantities or reduced activity of the monoamine neurotransmitters (e.g., serotonin, norepinephrine, and dopamine) within the brain. This etiology is supported by evidence that drugs that restore chemical imbalances in the levels of neurotransmitters in the brain effectively mitigate symptoms of depression. All antidepressants, in fact, achieve their effects by inhibiting the body's reabsorption or inactivation of monoamine neurotransmitters, thus allowing the neurotransmitters to accumulate and remain in contact with their receptors for prolonged periods of time; these changes seem to be important in elevating mood and relieving depression.

Classification of antidepressant:-

Antidepressants can be divided into five main types:

SNRIs: are used to treat major depression, mood disorders, and possibly but less commonly attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, menopausal symptoms, fibromyalgia, and chronic neuropathic pain.

SNRIs raise levels of serotonin and norepinephrine, two neurotransmitters in the brain that play a key role in stabilizing mood.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants. They are effective in treating depression, and they have fewer side effects than the other antidepressants.

SSRIs block the reuptake, or absorption, of serotonin in the brain. This makes it easier for the brain cells to receive and send messages, resulting in better and more stable moods.

They are called "selective" because they mainly seem to affect serotonin, and not the other neurotransmitters.
SSRIs and SNRIs may have the following side effects:

- Hypoglycemea or low blood sugar
- low sodium
- Nausea
- Rash
- Dry mouth
- Constipation or Diarrhea
- Weight loss
- Sweating
- Tremor
- Sedation
- Sexual dysfunction
- Insomnia
- Headache
- Dizziness
- Anxiety and agitation
- Abnormal thinking

Tricyclic antidepressants (TCAs) : Tricyclic antidepressants (TCAs) are so named because there are three rings in the chemical structure of these medications. They are used to treat depression, fibromyalgia, some types of anxiety, and they can help control chronic pain.

Tricyclics may have the following side effects:

- seizures

- Insomnia
- Anxiety
- Arrhythmia, or irregular heartbeat
- Hypertension
- Rash
- Nausea and vomiting
- Abdominal cramps
- Weight loss
- constipation
- Urinary retention
- Increased pressure on the eye
- Sexual dysfunction

Examples include amitriptyline (Elavil), amoxapine- clomipramine (Anafranil), desipramine (Norpramin), doxepin (Sinequan), imipramine (Tofranil), nortriptyline (Pamelor), protriptyline (Vivactil) and trimipramine (Surmontil).

Monoamine oxidase inhibitors (MAOIs)

This type of antidepressant was commonly prescribed before the introduction of SSRIs and SNRIs.

It inhibits the action of monoamine oxidase, a brain enzyme. Monoamine oxidase helps break down neurotransmitters, such as serotonin.

If less serotonin is broken down, there will be more circulating serotonin. In theory, this leads to more stabilized moods and less anxiety.

Doctors now use MAOIs if SSRIs have not worked. MAOIs are generally saved for cases where other antidepressants have not worked because MAOIs interact with several other medications and some foods.

Side effects include:

- Blurred vision
- Rash
- Seizures
- Edema
- Weight loss or weight gain
- Sexual dysfunction
- Diarrhea, nausea, and constipation
- Anxiety
- Insomnia and drowsiness
- Headache
- Dizziness
- Arrhythmia, or irregular heart rhythm
- Fainting or feeling faint when standing up
- Hypertension, or high blood pressure

Examples of MAOIs include phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan) and selegiline (EMSAM, Eldepryl).

Noradrenaline and specific serotoninergic antidepressants (NASSAs)

These are used to treat anxiety disorders, some personality disorders, and depression.
Possible side effects include:

- Constipation
- Dry mouth
- Weight gain
- Drowsiness and sedation
- Dlurred vision
- Dizziness

More serious adverse reactions include seizures, white blood cell reduction, fainting, and allergic reactions.

Examples include Mianserin (Tolvon) and Mirtazapine (Remeron, Avanza, Zispin).

HISTORY

MAOIs are the first class of antidepressant that were used to treat depression and were discovered largely by serendipity. As an example, the MAOI iproniazid was derived in the 1950s from an antibiotic that was ineffective for T.B but effective for depression. Examples, emsam (selegiline), marplan (isocarboxazid).

SSRIs are the first line treatment in the major depression introduced in the 1980s, and shortly thereafter they became some of the most commonly used antidepressants, primarily because they have fewer side effects than tricyclics or MAOIs.

Examples ,Celexa (citalopram), lexapro (escitalopram),luvox (fluvoxamine).

Also in the 1950s the first tricyclic antidepressants were discovered. These agents, so called because they are composed chemically of three carbon rings, inhibit the active reuptake, to varying degrees, of norepinephrine, serotonin, and dopamine in the brain. Examples, anafranil (clomipramine), asendin (amoxapine), elavil (amitriptyline), norpramin (desipramine).

SNRIs firstly introduce in france in 1996. Examples, cymbalta (duloxetine), fetzima (levomilnacipran).

Atypical antidepressant these are new drugs that do not fit in to any of the above- listed categories. Broadly described as atypical antidepressants, they affect serotonin, norepinephrine, and dopamine levels in unique ways. Examples , wellbutin (bupropion), remeron (mirtazapine), symbax, oleptro (trazodone).

How antidepressants work

It's thought that antidepressants work by increasing levels of a group of chemicals in the brain called neurotransmitters. Certain neurotransmitters, such as serotonin and noradrenaline, can improve mood and emotion, although this process isn't fully understood.

Increasing levels of neurotransmitters can also disrupt pain signals sent by nerves, which may explain why some antidepressants can help relieve long-term pain.

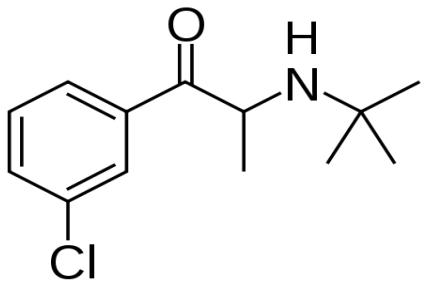
While antidepressants can treat the symptoms of depression, they don't always address its causes. This is why they're usually used in combination with therapy to treat more severe depression or other mental health conditions caused by emotional distress.

Introduction of Bupropion:

Bupropion is a low molecular weight compound (formula weight of HCl salt = 276.2), which has been in therapeutic use as an antidepressant since 1989. Its basic mode of action remains unknown. Much evidence points to modulation of dopaminergic and noradrenergic signaling. The use of bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL® and Zyban®, GlaxoSmithKline) in depression, smoking cessation, and various off-label treatments appears to be growing. This paper is a review of bupropion's clinical spectrum of action, basic pharmacology and current position in drug therapy and offers a potential mode of action based on the reviewed drug. Bupropion (Wellbutrin®) was approved by the FDA in 1989 for the treatment of MDD with the aim to improve efficacy and safety. Bupropion IR requires three daily doses; thus, to reduce daily dosing regimens, the sustained-release (SR) and extended-release (XL) were developed and approved by the FDA in 1996 and 2003.

Bupropion may be acting by augmenting the dopaminergic reward function. Better results are obtained when it is combined with nicotinic patch. The nicotinic withdrawal symptoms were less severe in bupropion recipients. However long –term efficacy is not known, while it can cause insomnia, agitation, dry mouth and nausea, but not sexual side effects. Seizures occur in over dose and in predisposed patients due to lowering of seizure threshold. It is contraindicated in eating and in bipolar illness. Bupropion is infrequently used to treat depression except those with atypical features, or it may be added to a SSRI as an augmenting drug. It is not suitable for treatment of anxiety disorder.

Structure



Synonym- Bupropion Hydrochloride

Chemical name - (±)-2-(tert-Butylamino)-1-(3-chlorophenyl)propan-1-one

Mol.formula-$C_{13}H_{18}CINO$

Mol.wt.-239.74 g/mol

Melting range-270-272 ^{0}c

Pka-7.6

Storage- Prior to dispensing, store in refrigerator at 36° to 46°F. Protect from heat and moisture.

Category- Atypical anti- depressant

MECHANISM OF ACTION

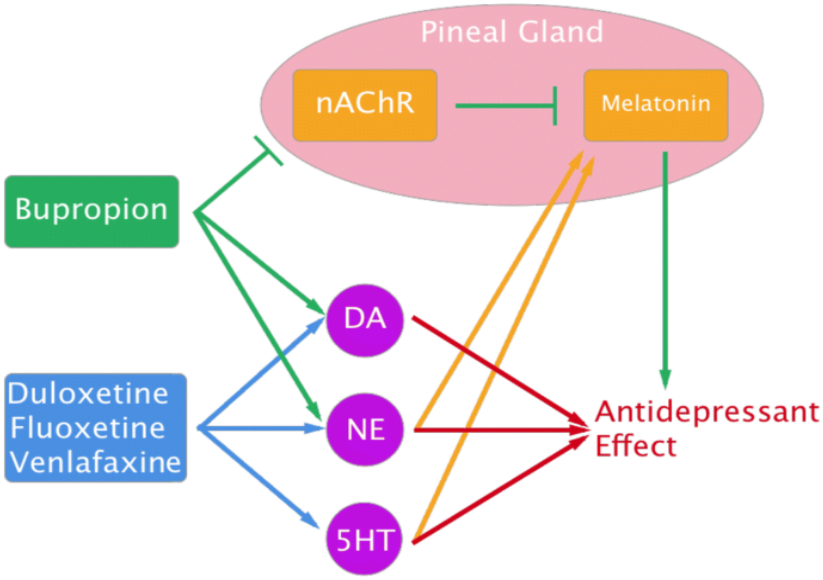


Figure 1:

PHARMACOKINETIC

Bupropion is metabolized by liver (approx.21hr). The primary active metabolite is 4-hydroxybupropion formed by cytochrome P450(CYP)2B6. After oral administration, bupropion is rapidly absorbed reaching the peak blod plasma concentrationafter1.5hr. Bupropion bioavailability is unknown but is presumed to be low due to first pass metabolism. The bupropion is metabolized in the body by different pathways. Cytochrome P450 is by oxidative pathway CYP2B6 isoenzymes leading to R,R- and S,S- hydroxybupropion and, to a lesser degree, CYP2C19 leading to 4'-hydroxybupropion. 11B- hydroxysteroid dehydrogenase in reductive pathways in liver and intestine leading to AKR7A2/AKR7A3 leading to threo-hydrobupropion. Further study is describe that bupropion is metabolized by 2 major carbonyl reductases to form threohydrobupropion and erythrobupropion. Carbonyl reductase enzymes are found to be highly polymorphic. These enzymes changes through the GIT, liver. CYP2C19 and CYP3A4 are important for bupropion metabolism but these are less characterized as compared to carbonyl reductase and CYP2B6.

DOSE

The starting dose of bupropion is 150mg/day then increase dose gradually to reduce the risk of seizure. After 3 week increase the dose as 300mg/day, as 150mg/twice a day with the interval at least 8hr. Maximum dose of bupropion is 400 which is given 200mg/twice a day. The 400 dose is given those patient who are not responding on 300mg/day.

Overdose

Overdose of bupropion result in clinical effects in over 1/3 of cases. The common symptoms of bupropion overdose is hypertension, nausea, sinus tachycardia, vomiting, drowsiness, agitation, and delirium and seizures. Less common symptoms which found less in patient is arrhythmia, coma, visual hallucination, ECG changes. In teenagers and adults seizure are more observed with the increasing seizure rate with dose of 600mg/day.

USES

Bupropion is mainly use to treat smoking cessation. Bupropion treatment course last for seven to twelve weeks, with the patient halting the use of tobacco about ten days in to the course. Bupropion approximately doubles the

chance of quitting smoking successfully after three months. Placebo- controlled double blind clinical studies have confirmed the efficacy of bupropion for depression. Bupropion has shown some success in in the treatment of social phobia and anxiety. Bupropion is the drug of choice for treatment of SSI- induced sexual dysfunction. It can improve mood and feelings of well- being. It may restore the balance of certain neurotransmitters in your brain.

Adverse effect

- Drowsiness
- Anxiety
- Difficulty falling asleep or staying asleep.
- Dry mouth
- Dizziness
- Headache
- Nausea

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