Overview of new anti-depressants

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Abstract This is a review of accumulated laboratory and clinical information on new anti-depressants, focusing on selective serotonin reuptake inhibitors, the serotonin and norepinephrine reuptake inhibi tor, reversible inhibitor of monoamine oxidase-A, and bupropion with particular emphasis on their pharmacokinetics, indications, dosages, precautions, adverse effects and drug interactions. We conclude that these new anti-depressants may offer improvement in side-effect profile and safety in overdose but not necessarily in the overall rate of improvement.

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Keywords:

Major depression is one of the most prevalent, serious illnesses in the world. It affects millions of people of all ages and from all walks of life, resulting in greater impairment than occurs with most chronic medical illnesses. Although this disorder can be devastating, it is now more treatable than ever before. Its many symptoms lead patients to seek care but unfortunately many cases go unrecognized. There are several myths that contribute to this problem. Depression may be considered as trivial, as likely to go away on its own, or a result of character weakness that demands greater self-control. It may be disguised by somatization and perhaps misdiagnosed.

An epidemiologic catchment area study indicates that major depression has a one month prevalence of 2.2% and lifetime prevalence of 5.8% in Americans 18 years and older and other studies have found lifetime prevalence as high as 25% for females. In Saudi Arabia, there are no epidemiological studies related to depression but there is no reason to believe that the incidence would be very different from Western countries. It has been suggested that the rate of depressive illness is increasing each year, but this is probably an artifact of better identification.

Over the past few decades, there has been growing interest in studies of depression. Recently, investigators extended the foci of outcome research to include measures of cost and long-term response to various treatments for major depression. Economists estimated the annual cost of work lost to depression in the U.S.A. at about $43 billion dollars.

Depression is a chronic and recurrent illness. It is estimated that over 50% of people who have an episode will eventually have another episode. The objectives of treatment are not only to decrease depressive symptoms and avoid self-harm or suicide, but also to reduce the risk of relapse and recurrence. Recently, significant advances have been made in the area of diagnosis (Table 1), pharmacotherapy and maintenance therapy.

 Treatment of depression should be conceptualized as a series of phases: acute, continuation and maintenance. The acute phase of treatment is directed to symptom remission. In the continuation phase the aim is to prevent relapse. During the maintenance phase the goal is to prevent recurrence. In clinical practice the boundaries of these phases are often blurred, but it is important to distinguish these phases to optimize treatment planning for the patient.

For the past 30 years, tricyclic anti-depressants (TCAs) have been the predominant first-line treatment for major depression. However, because of their side effects and potential for abuse, their use has been declining. Newer agents, such as the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitors (SNRIs), have been developed to provide a safer and more effective alternative to TCAs.

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Table 1: DSM IV Classification of mood disorders: (depression) with ICD-10 codes.

<table>
<thead>
<tr>
<th>Depressive Disorders</th>
<th>DSM-IV</th>
<th>ICD-10</th>
</tr>
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<tbody>
<tr>
<td>- Major depressive disorder</td>
<td>296.2</td>
<td>F32.X</td>
</tr>
<tr>
<td>- single episode</td>
<td>296.3</td>
<td>F33.X</td>
</tr>
<tr>
<td>- recurrent</td>
<td>300.4</td>
<td>F34.1</td>
</tr>
<tr>
<td>- Depressive disorder (unspecified)</td>
<td>311.</td>
<td>F32.9</td>
</tr>
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</table>

**Bipolar disorders**

- Bipolar I disorder
  - most recent episode depressed | 296.5  | F31.X  |
- Bipolar II disorder
  - most recent episode depressed | 296.89 | F31.8  |
- Cyclothymic disorder            | 301.3  | F34.0  |

**Other disorders**

- Mood disorder due to
  - [indicate general medical condition] | 293.83 | F06.XX |
  - with depressive features            | F06.32 |
  - with major depressive-like episode  | F06.32 |
  - Substance-induced mood disorder     |        |
  - with depressive features            | 292.84 |

Pharmacologic treatments for depression and monoamine oxidase inhibitors (MAOI) have been the second-line. More recently, there has been an explosion of research into serotonergic mechanisms in the neurobiology of depression. This led to the development of a new class of anti-depressants, the selective serotonin reuptake inhibitors (SSRI). Subsequently a further new class of drugs that selectively inhibit both serotonin and norepinephrine, (SNRIs) are being evaluated. The emergence of reversible inhibitors of the monoamine oxidase A enzyme (RIMA) agents also represents an advance in anti-depressant pharmacotherapy research. The relative advantages and disadvantages of each of these new classes of drugs have yet to be determined.

Anti-depressant drug therapy must be selected carefully since these drugs can produce significant side-effects that may affect treatment compliance. However, this is not a rationale for avoiding, delaying or under-prescribing drug therapy. Inadequate maintenance pharmacotherapy for depression is associated with substantial risk of recurrence. Untreated depression is also associated with increased social dysfunction, isolation, withdrawal, feelings of hopelessness and risk of further deterioration. In this paper, we will focus on the new psychopharmacological modalities available in the treatment of major depression including SSRI’s related compound, SNRI, RIMA and other novel agents.

**Selective serotonin reuptake inhibitors (SSRI)** This class of drug recently became the first-line treatment of major depression and other psychiatric disorders. The SSRIs are selective inhibitors of neuronal serotonin [5-hydroxytryptamine (5-HT)] reuptake. Serotonergic fibers originating in the dorsal and median raphe nuclei innervate numerous structures in the brain (cortex, hippocampus, striatum, amygdala, accumbens, substantia nigra, hypothalamus) as well as cells in the spinal column. Serotonin (5-HT) has the potential to influence numerous psychological, behavioral, cognitive, emotional and sensory functions. The 5-HT plays a role in a range of psychiatric disturbances: including unipolar depression, bipolar disorder, anxiety disorders, eating disorders, obsessive-compulsive disorder (OCD), panic disorder and “aggression”. It has even been suggested that this spectrum of illnesses may be thought of as “Serotonin Disorders”.

The SSRIs have been shown to increase 5-HT transmission in the rat brain following long-term administration. Two lines of clinical evidence indicate that the 5-HT system plays a pivotal role in mediating the antidepressant response in humans. First, the therapeutic effects of the TCA imipramine and the MAOI tranylcypromine were reversed by blocking 5-HT synthesis. Second, the addition of lithium to the therapeutic regimen of patients with resistant depression has been shown to produce a marked improvement in a significant proportion of people studied. Since lithium has been shown to enhance 5-HT transmission in biochemical, behavioral and electrophysiological studies in humans this supports the hypothesis that the 5-HT system underlies the neuro-biological basis of depression. However, the lithium’s augmentary action may not be through its effects on 5-HT. The SSRIs have minimal affinity for muscarinic, histaminergic, noradrenergic, or dopaminergic receptors. As a result, they lack the anticholinergic, hypotensive and cardiac side-effects associated with TCAs.

The SSRIs are well tolerated. Patients who don’t tolerate one SSRI may do well with another. The SSRIs are metabolized and excreted by the liver, and they are competitive inhibitors of cytochrome P450ID6, an hepatic isoenzyme which is important in the metabolism of various drugs, including TCAs, neuroleptics, benzodiazepines and anti-convulsants. This has clinical importance as concurrent administration of SSRIs with other drugs metabolized by the same route might increase the bioavailability of the other drugs in the blood. In a double-blind study, fluoxetine increased TCA plasma levels by two to
ten fold, and this effect can persist for weeks after the drug is discontinued. Clinical differences among the SSRIs may reflect the half-life of these agents. Fluvoxamine, paroxetine and sertraline have half-lives of 22, 20 and 26 hours, respectively. These compounds do not produce active metabolites. In contrast, fluoxetine has a half-life of 70 hours and its active metabolite, norfluoxetine, has a half-life of 330 hours. This has clinical importance as a five week washout is required before switching over to a MAO inhibitor because of the risk of developing the serotonin syndrome. The SSRIs are relatively safe in overdose. There have been no reports of death associated with SSRIs overdose alone although there is a serious risk if the overdose includes an SSRI and a RIMA. It is important to emphasize that controlled data show that the SSRIs are no more likely than other anti-depressants to cause or exacerbate suicidal ideation. As a group, the SSRIs are frequently associated with gastrointestinal side-effects including nausea, vomiting and diarrhea. The incidence is between 20 and 25%. In addition, they can exacerbate lithium induced tremor and neuroleptic associated parkinsonism through their effects on the balance between serotonin and dopamine in the substantia nigra. The incidence of sexual dysfunction varies between 2.2 and 43% and is higher with sertraline than with fluoxetine and paroxetine. There are differences between individual SSRIs in side-effect profile. Fluoxetine tends to have more central nervous system side-effects including restlessness, akathisia, anxiety, headache and tremor. Also, fluoxetine can cause weight loss with >5% weight loss in about 13% of patients. Fluoxetine is also associated with a decrease in glucose concentration; therefore, diabetic patients should be carefully monitored as it may be necessary to decrease the dosage of their hypoglycemic drug. Rare cases of fluoxetine-associated hypotension have been seen in patients treated with diuretics who are also water-deprived. Fluvoxamine causes more nausea and vomiting than other SSRIs and is the only one that is a sedative. On the other hand, sertraline and paroxetine can cause insomnia or sedation and have a higher incidence of headaches.

In major depressive disorder the emerging data indicates that SSRIs are effective across the spectrum of depressive severity and subtypes. The majority of studies support the conclusions that SSRIs are equal in efficacy to TCAs and that SSRIs have a safer side-effect profile when compared with TCA's because of the lack of anticholinergic and cardiovascular effects, SSRIs are being used increasingly in the treatment of depression in medically ill patients.

For depression, the adult recommended dose of fluoxetine is 20 mg daily usually given in the morning because of the potential insomnia. Because of the long half-life of fluoxetine and its metabolites, it takes approximately four weeks to reach steady state plasma concentration. Although the anti-depressant effect often appears in the first three weeks of treatment, the clinician may have to wait up to six weeks before evaluating the anti-depressant activity. If no response is observed, the dosage may be increased by 10 or 20 mg daily every ten days up to a maximum dose of 60 mg daily.

Fluvoxamine is titrated with a starting dose of 50 mg daily, increasing to between 150 mg and 300 mg daily depending on the side-effects and clinical response. Increases can be every three days if side-effects are minimal. Fluvoxamine can be administered as a single evening dose to decrease its adverse effects.

For sertraline, the starting dose is 50 mg daily. This dose can be maintained up to three weeks and if there is no response, the dosage can be increased by 50 mg weekly up to a maximum of 200 mg daily.

Paroxetine's dose range is from 20 to 50 mg daily. The usual starting dose is 20 mg daily and the dose can be increased by 10 mg weekly when the patient fails to show an adequate response in one to three weeks.

Approximately 65 to 70% of patients will respond to the above dosages. Augmentation strategies can be used to increase the response rate. Lithium can be used as an augmenting agent (600-1200 mg daily). Patients usually show response within two weeks and if not, lithium should be discontinued. Cytomel or T3 is another drug used to augment SSRIs. The usual T3 dose is 25-50 mcg daily. Tricyclic anti-depressants, particularly desipramine, can be used in a low dose such as 50mg daily. Serotonin precursors particularly tryptophan have been used successfully in augmentation. Tryptophan can be used to augment TCA, or MAOI therapies. The usual recommended dosage is 2-6mg/day in divided doses. All the above agents can be used for a period similar to lithium augmentation. As a result a significant proportion of patients can be converted to treatment responders.

One of the most important recent developments in the management of depression is
the recognition of the need for long-term treatment. SSRIs must be continued after apparent response in an attempt to consolidate the response and prevent relapse. Therefore, treatment should continue for a period of at least six months after response of the acute episode in all patients with depression. In recurrent depression, patients should receive long-term, even life-time, maintenance treatment to decrease the risk of recurrence.

**SSRI use in geriatric depression** Selective serotonin reuptake inhibitors have demonstrated equal efficacy to tricyclics in geriatric depressed patients. Furthermore, they are significantly better tolerated. Although the pharmacokinetic data on the use of SSRI’s in the elderly are limited, it is suggested that the elderly require the same dose to produce equivalent plasma concentration. The major side-effects in the geriatric population resulting from SSRI’s are similar to those of young adults. The SSRIs should be maintained for a minimum of two years following an episode of depression because of significant risk of recurrence during this period.

**Other indications for SSRIs** A number of controlled and uncontrolled studies have been published suggesting that they are effective in other psychiatric conditions (Table 2).

In summary SSRIs provide effective treatment for the various subcategories of clinical depression, may treat a wide range of other potential indications, are well tolerated for short-term and for maintenance treatment, are well tolerated by the elderly, have low lethality in overdose, have minimal drug interactions (excluding MAOIs) and a long half-life which makes them suitable for once-daily dosing.

**Atypical antidepressant nefazodone** Nefazodone is a promising new modified SSRI antidepressant treatment. It is a phenylpiperazin analogue of trazodone. Clinical trials have demonstrated anti-depressant efficacy equal to tricyclics. Nefazodone has a dual mechanism of action. It acts as an SSRI and as a 5-HT2 receptor antagonist. It has a highly selective pharmacological profile with no anti-cholinergic activity, cardiotoxicity or affinity to histaminic receptors, and low affinity for α1-adrenergic receptors. There are two active metabolites, hydroxynefazodone which is as active as the parent compound and m-chlorophenylpiperazine which has some post-synaptic serotonin activity. Besides its use in adults, preliminary reports indicate that it might be effective and safe in elderly depressed patients. In clinical trials, nefazodone produced no increase in suicidal acts or suicidal ideation. In fact it was superior to placebo in reducing suicidal ideation. Nefazodone demonstrated efficacy in relieving symptoms of anxiety associated with major depression and was found to be effective in panic disorders. It can improve sleep quality by increasing sleeping time and REM sleep quality. Nefazodone reduced premenstrual symptoms in women with premenstrual dysphoric disorder. It is interesting to note that when combined with morphine it appears to potentiate analgesia without increasing lethality.

Since the drug is claimed to be relatively serotonin receptor specific, one would predict a fairly benign side-effect profile. However, several side-effects have been reported which appeared with significant difference from placebo including dry mouth, nausea, constipation, postural hypotension, asthenia, anxiety, uncoordination, dizziness, somnolence, visual field deficits, and abnormal vision. As in the case with all other classes of anti-depressants, nefazodone-induced mania may occur in bipolar patients.

The recommended dose of nefazodone ranges between 300-500 mg daily. As with other anti-depressants, the full anti-depressant effect may be delayed for four weeks or longer. Finally it should be noted that there are no systematic clinical trials addressing dose requirements in the elderly. However, it is recommended to start with 50 mg twice daily and titrate the dose based on clinical response.

**Serotonin and norepinephrine reuptake inhibitors (SNRI’s)** Venlafaxine hydrochloride belongs to a new class of anti-depressants [phenethylamines]. Venlafaxine has been shown to inhibit neuronal uptake of serotonin, norepinephrine, and to a lesser degree dopamine. Venlafaxine has almost no affinity for muscarinic,
cholinergic, histaminergic, or α1-adrenergic receptors. This drug has efficacy similar to TCAs, fluoxetine and trazodone. It is interesting to note that venlafaxine has more rapid onset of action than other anti-depressants in animal models.

Venlafaxine is well absorbed from the gastrointestinal tract. It is metabolized in the liver by demethylation to o-desmethylvenlafaxine which is active and pharmacologically similar to the parent compound. There are two minor metabolites, but they are less pharmacologically active. The half-life of venlafaxine is approximately three to five hours and of the active metabolite ten to eleven hours.

The side-effect profile of venlafaxine was compared with that of placebo; patients experienced five adverse effects at least 10% more often than placebo patients; nausea 35%, somnolence 24%, dizziness 18%, dry mouth 22% and seating 12%. A potentially serious adverse effect associated with venlafaxine is an increase in blood pressure especially in patients who are hypertensive at base line. It is important to note that the safety of venlafaxine in pregnant women is unknown.

The minimum effective dose of venlafaxine is 75 mg daily with a range up to 375 mg daily. Studies have shown efficacy is the same with b.i.d. dosages as with t.i.d. It may well turn out that once a day dosing is fine for many patients. The daily dose of venlafaxine can be increased by 75 mg each week. It is important to note that the dose should be reduced by half in patients with renal impairment.

**RIMA (Reversible inhibitor of monoamine oxidase-A)** The MAO inhibitors were introduced into psychiatry in the late 1950s as a treatment for depression. The identification of the two subgroups of MAO enzymes (A & B), with preferred neurotransmitter substrates led investigators to develop an agent which acts solely on MAO-A the enzyme which is primarily involved in serotonin and norepinephrine degradation. Moclobemide is one such compound which offers the clinician and depressed patient an alternative to TCA and SSRI therapies without significant dietary restriction. Brofaromine is another RIMA which has undergone extensive evaluation as an anti-depressant.

The agents produce selective and reversible inhibition of MAO-A. Moclobemide is a benzamide derivative that is structurally different from classical MAO-inhibitors. It has no affinity for muscarinic, dopaminergic, serotonergic, adrenergic, opioid or benzodiazepine receptors. In addition, it has no influence on diamine oxidase. There is reversible inhibition of the enzyme and as a result it has only a slight potentiating effect on the hypertensive action of tyramine. Moclobemide is 90% absorbed from the gastrointestinal tract after multiple doses. It is extensively metabolized mainly via oxidative pathways, and 95% of the dose is excreted in urine. Comparative studies of moclobemide showed that it has equal efficacy to TCAs with a better side-effect profile particularly less anti-cholinergic side-effects. However, observed adverse effects include dry mouth, tremor, sweating, constipation, blurred vision, insomnia, headache, restlessness and palpitation. Moclobemide does not inhibit sexual desire or performance and it seems that it does not worsen cognitive function. Unlike conventional MAO inhibitors, moclobemide is largely devoid of hepatotoxicity. It has shown possible interaction with lithium, TCAs, benzodiazepines, neuroleptics, levodopa and benzodiazepines. However, these interactions were not found to be of significant clinical concern. There is not enough data to evaluate the effect of moclobemide overdose, but early reports suggest that there have been no deaths from moclobemide overdose alone, though the combination with SSRI or clomipramine can be lethal.

In patients with a past history of bipolar affective disorder, caution is required in the treatment of the depressive phase as it too may provoke manic episodes. Moclobemide has been found effective in various psychiatric and non-psychiatric disorders including dysphoria, tardive akathisia, menopausal flushing, and migraine headache prophylaxis. Presumably because the pharmacokinetics of moclobemide are similar for young and old patients, studies have shown that elderly depressed patients tolerate moclobemide well with a low incidence of sedation and orthostatic hypotension.

Moclobemide has been used in attention deficit hyperactivity disorder in children. Initial reports indicate 30-40% improvement in patients who had previously discontinued methylphenidate because of side-effects. Moclobemide was well tolerated by these patients.

Follow up after one year of treatment with moclobemide suggests that it is effective, safe and well tolerated in long-term administration.

Moclobemide is excreted into breast milk in low amounts. However, it is unlikely to be hazardous to the suckling infant.
Bupropion Although bupropion was first synthesized in 1966, it was only approved in the USA for the treatment of depression in 1985. The association of this drug with liability to seizures has limited its use in the USA and it has not been approved in Canada. Later studies showed that the rate of seizure on bupropion falls within accepted parameters. Preclinical and clinical studies of bupropion have established the safety and efficacy of the drug.

Bupropion is a unique anti-depressant in its structure, with a mechanism of action that is not clearly understood. However, its ability to block neuronal dopamine reuptake is its most potent effect on neurotransmitter mechanisms, suggesting a markedly different anti-depressant mechanism from other anti-depressants. It has also been shown that bupropion treatment led to reduction of norepinephrine turnover. It appears that it does not appreciably inhibit the reuptake of serotonin or norepinephrine. In rat studies, hydroxybupropion which is the principal metabolite of bupropion, was found to produce β-adrenergic receptor down-regulation. The drug is well absorbed from the gastrointestinal tract particularly when in liquid form. The elimination half-life has been found to be 11.2 hours.

Bupropion undergoes extensive first-pass metabolism by hepatic enzymes. However, there are three principal metabolites which have substantially longer half-lives than the parent compound: hydroxybupropion (HB); threobupropion (TB); and erythrobupropion (EB).

Bupropion is an effective anti-depressant as demonstrated by several double-blind clinical trials. In addition, several reports have shown its efficacy in other psychiatric and non-psychiatric conditions. It has been found effective in the treatment of the depressive phase of bipolar affective disorder. Also, it was found to be effective in seasonal affective disorder and social phobia. Single reports have appeared about the use of bupropion in chronic low back pain, fatigue associated with multiple sclerosis, migraine headache, and chronic fatigue syndrome.

Although bupropion is relatively safe, seizures are a concern and the incidence is dose-dependent. Plasma level monitoring might increase the safety of the medication. The most common adverse effects are headache, tremor, insomnia, agitation, dizziness, constipation, nausea and vomiting, dry mouth and excessive sweating. However, there are reports of catatonia and of exacerbation of tics in children with attention deficit hyperactivity disorder and Tourette’s syndrome. Despite initial claims to the contrary, drug-induced mania has been reported in depressed bipolar patients treated with bupropion. Bupropion was found in breast milk in concentrations higher than the plasma level; in addition, it was found that its two metabolites are also excreted into milk. However, neither bupropion nor its metabolites were detected in the infant’s plasma but it is important to consider a possible effect as there are no studies published yet about the safety of the drug in pregnant or lactating women, as is true for most of these recently introduced drugs.

The drug has been tolerated up to 4200 mg a day without significant mortality or morbidity but there are reported cases of death in overdose secondary to seizure and cardiovascular collapse. The use of bupropion in the elderly has not been well studied. In the few double-blind studies of bupropion there were no reported differences of absorption or elimination in the elderly and the drug was therapeutically successful, with no significant adverse reactions. There are no studies of the safety of bupropion in children.

There are reports of significant drug interactions especially when using bupropion in combination with drugs that induce or inhibit hepatic drug metabolism. There have been reports of interaction with carbamazepine, fluoxetine, levodopa, lithium and alcohol. In combination with MAOIs there have been some significant adverse drug interactions. The dose of bupropion ranges from 100 to 450 mg but most commonly is 200 to 300 mg.

Summary In summary, we should emphasize that recent developments in the pharmacotherapy of depression has advanced our understanding of affective disorders. However, new anti-depressants may offer improvement in side-effect profile and safety in overdose but not necessarily in the overall rate of improvement. The better tolerability of these agents could produce better compliance with treatment and flexibility in using higher doses which might mean better quality of life. Although long-term trials of anti-depressants are limited, the likelihood is that long-term treatment might be necessary for many people with major depression to avoid the risk of recurrence.

While awaiting new, improved drugs we must continue to assess the benefits and limitations of the recently introduced agents discussed in this article.
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نظرة عامة على مضادات الإكتتاب الجديدة

هذه مراجعة للمعلومات السريرية والمخبرية المعروفة عن مضادات الإكتتاب الجديدة، تركز بصورة خاصة على موانع منتفئة إعادة امتصاص السيروتونين، موانع إعادة امتصاص مادتي السيروتونين والناورادربيلالين (اللاكتون)، موانع أحادي الأمين المؤكسدة (أو أفقابل للإرتداد، والسربوربيون. من حيث تأثيرها آليةها الدوائية، إستطباباتها، جرعتها الدوائية، تأثيراتها الجانبية الإضافية إلى تفاعلاتها مع الأدوية الأخرى. وصلنا إلى الاستنتاج بأن هذه المضادات الجديدة قد تخطى نتائج أفضل من حيث التأثيرات الجانبية والأمان في حالة تناول جرعات مفرطة وليس من الضروري أن تعطي نتائج أفضل في درجة تحسين المريض العامة.