New Developments in the Treatment of Depression 2008-2009

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Despite the development of new and sometimes novel treatments for depression, many patients achieve an inadequate response to currently available treatment. Results from the Sequenced Treatment Alternatives to Relieve Depression (Star*D) it is estimated that at least 20% of patients do not respond adequately to 4 consecutive and sometimes aggressive pharmacotherapies[1]. In addition, patients who do not achieve remission with the first or second pharmacotherapy trial will tend to relapse within 12 months even when they ultimately do achieve a remission level response[2]. Thus, there remain substantial gaps in the treatment of depression.

Few new antidepressants have been released since 2007. Desvenlafaxine (Pristiq) was approved in 2008 for the treatment of major depression. Desvenlafaxine represents the major metabolite of venlafaxine and joins other serotonin – norepinephrine reuptake inhibitors (SNRIs) including duloxetine[3]. Desvenlafaxine appears to be a stronger norepinephrine reuptake inhibitor at therapeutic doses than does venlafaxine and less noradrenergic than is duloxetine. Unlike venlafaxine, desvenlafaxine is not substrate of CYP450 2D6 isoenzyme and does not undergo extensive hepatic metabolism [4]. These differences in metabolism may suggest somewhat few risks for certain drug interactions than with venlafaxine. The efficacy data indicate that desvenlafaxine is superior to placebo in relieving depressive symptoms[5]. Comparison efficacy studies with other antidepressants, including venlafaxine have not been completed and there is no evidence it is more or less effective than other antidepressants. As with all new drugs, there is a cost disadvantage of desvenlafaxine relative to generic antidepressants. Reported side effects are comparable to other SNRIs.

Milnacipran is an additional SNRI the FDA approved in 2009 for the treatment of fibromyalgia. While not approved for the treatment of major depression, milnacripan has been extensively studied in the treatment of depression and approved as an antidepressant in Europe[6]. Most studies have concluded that milnacipran is as effective as the SSRIs or Tricyclic antidepressants and better tolerated than tricyclic drugs[7]. Like desvenlafaxine, there are few pharmacokinetic drug interactions. However, there are no clear side effect or efficacy advantage relative to other SNRIs.

While combination pharmacotherapy or augmentation is common in clinical practice, until 2007 there were no FDA approved adjunctive treatments for major depression. The first agent approved in the adjunctive treatment of depression was the second generation antipsychotic aripiprazole (Abilify). Several randomized controlled trials have demonstrated the utility of aripiprazole added to standard antidepressants relative to adjunctive placebo at doses in the 5-15 mg/day range [8],[9]. The randomized trials have been of about 6 weeks duration for the combination portion of aripiprazole added to an antidepressant. The side effects of aripiprazole added to an antidepressant are comparable to its side effects in other indications [10]. However, akithisia has been reported at higher rates (25%) than is typically reported in schizophrenia or bipolar studies and long term safety data of adjunctive aripiprazole in the treatment of major depression is unavailable.

In 2009, the combination of olanzapine and fluoxtine (OFC;Symbyax) was approved for the treatment resistant depression. A number of studies have compared the combination of olanzapine to monotherapy with fluoxetine or olanzapine alone in patients who had failed one or more previous medication trials [11],[12]. The efficacy of 8 weeks of the combination drug was superior to the efficacy of monotherapy with fluoxetine or olanzapine. Side effects of the combination were similar to what would be expected from the individual drugs except a somewhat higher total cholesterol in the OFC group. Not all studies have shown superiority of OFC over monotherapies. Studies that have compared OFC with nortriptyline[13] and venlafaxine [14] monotherapy in a resistant population have not demonstrated advantage of OFC at the endpoint.

An FDA advisory panel reviewed the data of quetiapine in the monotherapy and adjunction treatment of major depression in 2009. While there was general agreement that the submission supported the efficacy of quetiapine in the monotherapy of depression, concerns were raised by the panel about the relative risk vs. benefit of quetiapine as a monotherapy for first line treatment of depression [15],[16],[17]. Thus, they advised against approval of quetiapine monotherapy for depression. On the other hand the advisory panel did feel that the use of adjunctive quetiapine was justified in a treatment resistant depression population. As of this writing, the FDA has not approved adjunctive quetiapine in the treatment of depression. As with other SGAs used in the treatment of depression, there is no comparison efficacy data and little long term safety data of the use of quetiapine in the treatment of major depression.

Two devices have previously been approved for the treatment of major depression. Electroconvulsive therapy (ECT) has been used for 70 years and ECT devices were grandfathered in without a specific approval process. In 2009, the FDA announced it was re-reviewing grandfathered devices, including ECT devices, and

might require formal approval for these devices. Thus, controlled clinical trials might be required for specific ECT devices. The second device approved for the treatment of depression is Vagus Nerve Stimulation (VNS), was approved in 2004. Its use appears to be limited at this time secondary to both questions about the adequacy of the clinical trial and the failure of third party coverage for the treatment of depression. In late 2008, the FDA approved the use of transcranial magnetic stimulation (TMS) for the treatment of depression. TMS uses a focused electromagnetic field to stimulate superficial cortical tissue. The pivotal clinical trial compared active TMS at 3000 pulses/session 5 times/week for 6 weeks vs. sham treatment[18]. The approximately 300 patients who participated in the trial had depressive episodes of less than 3 years duration, had failed to respond to 1-4 medication trials, and were not on medications in the trial. At the end of 4 and 6 weeks about 25% of patients in the active group has a 50% response on the Hamilton Depression scale or Montgomery Asberg Depression scale vs. about 12-15 % response in the sham treatment. Likewise, remission rates were about 14-17% for the active group vs. 5-8% for the sham control group. Side effects tended to be mild and included discomfort around the site of application, eye pain and headache. There is no published safety or efficacy data after 6 weeks treatment with the approved (Neuronetics) device. Reviews of TMS trials in the treatment of depression have generally concluded that TMS efficacy in treatment resistant depression is modest to moderate [19],[20].

Thus, there are a number of potentially important developments in the treatment of depression since 2007. New medications and devices provide more options although it is not clear that these represent better options than previously available pharmaceuticals or devices. In most cases, the newer treatments are more costly without necessarily being more effective. However, there may be other advantages to the newer treatments including tolerability that make them attractive interventions in some patients.

New FDA Developments in the Treatment of Major Depression since 2007

Table 1. New SNRI Approvals

Medication	Indication	Dosage Range
• Desvenlafaxine	Major Depression	50-100 mg/day
• Milnacipran	Fibromyalgia	100-200 mg/day

Table 2. Adjunctive/Combination Treatments for Major Depression

Medication	Indication	Dosage Range
• Aripiprazole	Adjunctive use in depression	5-15 mg/day
• Olanzapine/Fluoxetine	Treatment-resistant depresssion	3/25 -6/50 mg/day
• Quetiapine (Pending Approval)	Adjunctive use in MDD	50-300 mg/day

Table 3. Devices for the Treatment of Major Depression

Treatment	Indication
• Electroconvulsive therapy	ECT devices to require formal approval and re-assessment for a specific indication in the treatment of MDD
• Transcranial Magnetic Stimulation	Neuoronetics device approved for the treatment of depression after depression in patients who have not responded to drug therapy

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