Update on Recent Development in the Treatment of Depression 2011

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Summary of Key Developments in the Treatment of Depression

Pharmacotherapy

- Increasing availability of generic antidepressants including escitalopram in 2012
- Introduction of the partial 5HT1a agonist/ SSRI Vilazodone for the treatment of depression
- Co-Med trial, which failed to show an advantage of combining antidepressants over monotherapy to improve outcome in the initial acute treatment of MDD.

Devices

- Additional TMS data suggesting the benefits of longer duration of treatment, and the possible value of R sided low frequency treatment particularly in bipolar and anxious patients.
- Limited VNS data confirming some of the previous data on efficacy.
- The current review by the FDA of ECT devices as category III devices that could impact the availability of ECT as an option for resistant depression

APA Guidelines for the Treatment of Major Depressive Disorder (3rd Ed, 2010)

- The use of rating scales to monitor patient status
- The use of TMS, VNS, MAOIs as well as ECT in resistant depression
- The need for longer maintenance treatment in recurrent depression
- The value of exercise in the elderly and those with co-morbidities.

In the past 2 years, there has been incremental progress in the treatment of major depression. Regulatory burdens, the increased availability of good generic agents, and the increased cost of developing pharmacological agents has resulted in a dramatic slowing of new antidepressants being introduced. In 2012, the last brand name SSRI, escitalopram (Lexapro) will go generic. In addition a number of agents approved in the adjunctive use of depression including quetiapine and olanzapine are expected to have generics in 2012. There have been a number of studies that help guide the clinician in treatment and APA updated the depression guidelines in 2010 for the first time in 10 years.

The only new antidepressant to be approved since 2009 is vilazodone (Viibryd). Vilazodone is a partial agonist of the 5HT1a receptor and a selective serotonin reuptake inhibitor. Two randomized placebo controlled trials of over 400 subjects each demonstrated that a dose of 40 mg/day of vilazodone was more effective than placebo in reducing symptoms of depression on standard depression scales (MADRS, Ham D) [1, 2]. There is no evidence that vilazodone is more or less effective than any other antidepressant. The side effect profile may be favorable in some patients as the rate of sexual side effects appears to be lower than many other agents (4% rate of sexual dysfunction vs. 1% on placebo) and appeared weight neutral in the acute trials. On the other hand the GI side effects may be greater than other antidepressants. Vilazodone is a substrate of the CYP 3A4. Thus the dose of vilazodone should be cut in half when concurrently using ketoconazole or erythromycin. On the other hand it a mild inducer of 3A4 and 2C19 isoenzyme so The most common side effects were diarrhea (which occurred in 28% of subjects vs 9% in placebo) and nausea (23 vs. 5%) vomiting (5% vs. 1%). The dose of

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vilazodone should be started at 10 mg/day then increased to 20 mg/day for 7 days, followed by the target dose of 40 mg/day.

Among the more important studies funded by the NIMH the past 2 years is the Combining Medications to Enhance Depression Outcomes (Co-Med) Study [3]. Given that remission rates for major depression in acute clinical trials are so low (30-35%) this study was undertaken to determine if a combination of antidepressants from the beginning of therapy might enhance remission rates. A total of 665 patients at six primary care and nine psychiatric sites with moderate to severe, recurrent MDD were randomized to one of three treatment groups; escitalopram (up to 20 mg/day) plus placebo, escitalopram plus bupropion SR (up to 400 mg/day), and venlafaxine XR(up to 300 mg/day) plus mirtazapine (up to 45 mg/day). Subjects were treated for 12 weeks acutely and then followed up for up to 7 months in continuation treatment. The results of the acute treatment did not show any advantage for the combination treatment groups over the escitalopram alone. All three groups had about a 38% remission rate and 51-52% response rates. Likewise, at 7 months there was no advantage for the combination treatments over monotherapy with escitalopram in response or remission rates. Thus, this study suggests that there may not be an advantage to starting two antidepressants together over just using one. However, the StarD study [4] did suggest that there may be an advantage of adding another antidepressant if acute treatment with one antidepressant failed to achieve a remission.

Devices are playing a somewhat larger role than they have in the recent past with the approval of Transcranial Magnetic Stimulation (TMS) and Vagus Nerve Stimulation (VNS) in the past decade. There were no major studies of VNS in the past 2 years. One naturalistic study of VNS in 75 European patients with resistant MDD followed for 2 years after implant suggested a somewhat better remission (39%)and response rate 53% than has been previously reported [5]. However, a recent meta-analysis of VNS studies completed to 2011 concluded that much of the response to VNS might be related to lower baseline severity of depression [6]. Patients who are less ill appear more likely to respond to VNS than patients with higher baseline severity. While, not surprising, severity of depression and resistance to treatment is the primary indication for VNS. Thus, the authors of the meta-analysis concluded that the studies of VNS in the treatment of depression to date are still insufficient to rule out that the response might be attributed to a placebo effect.

The FDA approved Transcranial Magnetic Stimulation (TMS) therapy in late 2008 for the treatment of depression that had not responded to at least one adequate medication trial. Despite the approval questions remain about the efficacy of TMS, and the optimal parameters, dose and duration of treatment. A number of studies over the past two years have added to our understanding of TMS in the treatment of depression although large gaps still exist. A recent meta-analysis of TMS studies concluded while the efficacy of TMS has been variable, more recent studies that have had durations of treatment greater than two weeks have generally been more effective than shorter trials[7]. In fact the mean number of TMS treatments required for response in one study was 26 which is considerably higher than the number of treatments in most studies [8]. A number of trials have also begun to suggest the low frequency (1 Hz, 600 pulses)

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on the right dorsolateral prefrontal cortex may be as effective as the standard left sided high frequency (10Hz, 3000 pulses)[9].Low frequency right sided treatment may also be an effective alternative in patients with higher levels of baseline anxiety and bipolar depression.[9, 10] In addition, bilateral TMS may be an option in patients who have not responded to the FDA approved left sided treatment[11, 12]. While the standard FDA protocol calls typically involves treatments 5x/ week, there is not necessarily any difference in efficacy if the treatments are done only 3x/ week[13].

Electroconvulsive therapy remains the gold standard in resistant depression. ECT appears to be substantially more effective than TMS in resistant depression but with greater side effects including cognitive problems [14, 15]. ECT devices where grandfathered in before the current device standard established the requirement for randomized controlled trials to demonstrate the safety and efficacy of a given device. In 2009, the US Government Accountability Office, which audits government agencies, urged the FDA to lift the grandfather clause that exempted ECT and other devices level III devices. In January of 2011, an FDA neurological devices advisory panel advised the FDA that ECT devices remain a category III device. The FDA is expected to rule on ECT devices in 2012. While the APA has encouraged the FDA to make ECT devices level II, upholding the level III status would force the manufacturers to conduct adequate randomized controlled trials of ECT before the devices could be approved. Since such a ruling would functionally preclude the current use of ECT as a treatment for resistant depression, the FDA is weighing options before ruling.

In 2010 the American Psychiatric Association published the first update in 10 years on its Guidelines for the Treatment of Patients with Major Depressive Disorder [16]. The APA group reviewed the MDD literature between January of 1999 and December of 2006 to come up with its recommendations and 1170 references were specifically cited in the document. While the review was quite comprehensive there were of notable changes from the second edition of the guidelines published in 2000. Among the key recommendations from the third edition include

- The use of clinician rating scales such as Hamilton depression Scale(HamD), Montgomery Asberg depression Scale (MADRS), or the Patient Health Questionnaire (PHQ-9) to monitor the progress of patients.
- The use of augmenting strategies, MAOIs, TMS, and VNS in resistant depression as well as ECT.
- The affirmation of the equal benefits of psychotherapies (including CBT, interpersonal, and problem solving therapy) to pharmacotherapy in mild to moderate depression and the benefits of the combination of psychotherapy and pharmacotherapy in moderate to severe depression. Psychotherapy alone is not recommended for patients with psychotic features or more severe depression.
- Aerobic and resistance training for helping depression particularly in the elderly and those with co-morbidities
- The need for longer durations of maintenance treatment particularly those with recurrent depression

As with the second edition, the choice of a starting antidepressant is largely based on

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factors such as drug interactions, cost, side effect profile rather than efficacy. The SSRIs, SNRIs, bupropion are recommended as first line treatments with TCAs and MAOIs used primarily in patients who have not responded to first line treatments or in special populations (such as TCAs for hospitalized patients).

Thus, the past 2 years have seen incremental additions to our understanding of the treatment of depression and the options available to us as clinicians. While the number of new medications introduced for the treatment of MDD is expected to further slow, novel agents continue to be investigated including glutamate modulators and triple reuptake inhibitors as well as additional devices such as Deep Brain Stimulation (DBS) will be further investigated in the next 24 months.

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