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Antidepressant Use In Bipolar Disorders – ISBD Recommendations

Because the use of antidepressants in bipolar disorders is controversial, the International Society for Bipolar Disorders (ISBD) convened a task force to seek consensus on this topic. Information was obtained from a literature search for studies published on antidepressant treatment in bipolar disorders. Monotherapy with antidepressants for bipolar disorder is contraindicated because of the weak evidence for efficacy and the potential risk for excessive mood elevation (switches). EMBOLDEN II (Efficacy of Monotherapy Seroquel in Bipolar Disorder) is the largest trial to date for monotherapy in which paroxetine was compared to quetiapine and placebo. Overall, studies do not support the use of antidepressants as monotherapy, with evidence being poor and inconclusive.

Short-term trials of adjunctive antidepressants for acute treatment of bipolar disorder with depression have reported mixed results. Available evidence supports the use of olanzapine/fluoxetine combination, indicates a lack of positive effects of paroxetine or bupropion added to mood stabilizers, and is otherwise inconsistent. Adjunctive antidepressants for long-term maintenance studies were also reviewed. Only two randomized trials lacking placebo controls have examined the effects of long-term antidepressant use for bipolar I depression. Conclusions were that evidence is limited and inconclusive to support the use. The assessment of antidepressant-associated mood switches into hypomania, mania, or mixed states was also reviewed. Risk of mood switching is higher and more severe in bipolar I than bipolar II patients and somewhat greater with the older antidepressants (and some SNRIs) in comparison to SSRIs.

The task force concluded that the use of antidepressants to treat depressive phases or components of bipolar disorder can neither be condemned nor endorsed without carefully evaluating individual cases and circumstances. The intention of this ISBD task force was to determine how best to use antidepressants to treat patients with bipolar disorder. Their recommendations are noted below.

Acute Treatment

- May be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants.
- Should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling.

Maintenance Treatment

- May be considered if a patient relapses into a depressive episode after stopping antidepressant therapy.

Monotherapy

- Should be avoided in bipolar I disorder.
- Should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms.
- Bipolar patients starting antidepressants should be closely monitored for signs of hypomania or mania and increased psychomotor agitation, in which case antidepressants should be discontinued.
- Should be discouraged if there is a history of past mania, hypomania, or mixed episodes emerging during antidepressant therapy.
- Should be avoided in bipolar patients with high mood instability or with a history of rapid cycling.
- Should be avoided during manic and depressive episodes with mixed features or those with predominantly mixed states.
- Should be discontinued in patients currently experiencing mixed states.

Drug Class

- Adjunctive treatment with SNRIs, tricyclics, and tetracyclics should be considered only after other antidepressants have been tried and the patient should be closely monitored because of an increased risk of mood switch or destabilization.

Pacchiarotti I, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013 Nov 1;170(11):1249-62.

Treatment for Alcohol Dependence: Gabapentin

The authors of this study set out to determine if gabapentin could increase the rates of sustained abstinence and no heavy drinking and decrease alcohol-related insomnia, dysphoria, and craving (all

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Atypical Antipsychotics Abused

Atypical antipsychotics are not typically thought to be medications anyone would want to abuse but, according to presenter Deborah L Haller, PhD, at the American Academy of Addiction Psychiatry's 24th Annual Meeting and Symposium, they are now being used to enhance the effects of other abused drugs or to counteract the effects of illicit substances. Surveys in the author's treatment center found that all atypical antipsychotics were abused, but quetiapine was by far the most abused. Typically, these medications are being obtained from family, friends, or a dealer. Most commonly, these were reported as being used with alcohol, opioids, and cocaine. Users reported the leading reasons for abusing atypical antipsychotics were to mellow or to slow down, believing that these medications limit withdrawals as they attempt to self-detox from other addictive substances. Some addicts experience unwanted effects, such as hallucinations or delusions, and they begin using antipsychotics to limit those effects. As marketing of atypical antipsychotics has expanded beyond the treatment of psychosis, the availability of these products has increased.

Dr. Haller suggests that physicians screen their patients for substance abuse before prescribing an atypical antipsychotic and be wary of patients requesting specific agents, especially if they have no history of requiring these medications. Patients who are prescribed these products should be made aware that they need to carefully and securely store them, especially if they have close contact with substance abusers.

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Gabapentin (cont.)

have been identified as risk factors for relapse) in a dose-dependent manner. Clinical findings indicate that gabapentin normalizes the stress-induced gamma-aminobutyric acid (GABA) activation in the amygdale that is associated with alcohol dependence. Mason and her team note that less than 9% of alcoholics are given Food and Drug Administration (FDA)-approved prescription medications to assist them during early abstinence and they believe that gabapentin has the potential to fill a large gap in the treatment of alcohol dependence. (Note: gabapentin does not currently have FDA-approval for the treatment of alcohol use disorders.)

The study was a 12-week, double-blind, placebo-controlled, single site randomized trial of 150 men and women older than 18 years with current alcohol dependence. Placebo, gabapentin 900mg per day, or gabapentin 1800mg per day were the three arms of the parallel groups. The authors hypothesized that gabapentin would be associated with significant linear dose-related increases in rates of sustained abstinence and no heavy drinking and decreases in symptoms involving mood, sleep, and craving. Results showed that gabapentin significantly improved the rates of abstinence and no heavy drinking with rates of 4.1% in the placebo group, 11.1% in the 900mg group, and 17% in the 1800mg group. In addition, the drug reduced cravings, depression, and sleeplessness. Sixty-five participants completed an additional 24-week follow-up visit showing a sustained effect of drinking outcomes.

Limitations to the study included a single site in an affluent community in Southern California. The results may not generalize to all treatment settings and alcohol-dependent populations. Secondly, the participants reported their own data assessed in a daily record. It is difficult to be sure that all participants precisely measured each and every drink they consumed and accurately documented these measurements. Lastly, the dropout rate was significant; however, the authors argue that the dropout rate was comparable to other randomized controlled trials involving acamprosate.

Mason BJ, et al. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Inter Med*. 2013 Nov 4. [Epub ahead of print].

Prophylactic Treatment of Interferon-alpha Associated Depression

The standard treatment for chronic hepatitis C (CHC) infection for the past decade has been pegylated interferon-alpha in combination with ribavirin (IFNR), as recommended in the guidelines from the American Association for the Study of Liver Diseases. The depression associated with IFNR is characteristic of a serotonergic deficiency with changes in the serotonin signaling pathway and, therefore, requiring the administration of SSRIs. Two protease inhibitors, boceprevir and telaprevir, have been granted FDA approval as adjunctive therapy, but only for individuals with genotype-1 infections. (It is believed that, if and when protease inhibitors become standard treatment, the rates of depression will decrease.)

The rate of mild to moderate depressive episodes in patients treated with IFNR has been found to be approximately 70%, while there is generally a 20-40% incidence of major depression in patients with the hepatitis C virus. This is a concern because IFNR-associated depression can lead to deterioration in quality of life and is noted as a major contributor to treatment withdrawal, non-compliance, dose reduction of IFNR, and even attempted suicide – all of which can result in treatment failure. Whether antidepressant prophylaxis is necessary in this population remains a subject of debate and prompted the authors of the articles to research published literature and conduct these recent meta-analyses. Noted in the articles are the following points:

- Depressive symptoms are closely related to poor virological response.
- Prophylactic and concomitant therapy with SSRIs can significantly reduce the incidence of IFNR-associated depression in patients with CHC. The most beneficial effects were found for citalopram and escitalopram.
- Prophylactic treatment reduced the emergence of depression in at least 12 studies.
- SSRI interventions did not negatively decrease the sustained virological response.
- SSRIs did not influence the rate of IFNR discontinuance and treatment withdrawal. There appears to be no clear indication that prophylactic therapy serves to boost treatment completion as compared to the monitor-and-rescue strategy.
- A recent hypothesis is that serotonin-acting antidepressants have an effect upon tumor-necrosis factor-alpha and interleukin-6, as well as other inflammatory markers.
- Risk factors for IFNR-induced depression are pre-existing psychiatric disorders, especially pre-existing depressive symptoms.

Hou X-J, et al. Can antidepressants prevent pegylated interferon-alpha/ribavirin-associated depression in patients with chronic hepatitis C: meta-analysis of randomized, double-blind, placebo-controlled trials? *PLOS ONE*. 2013 Oct 30;8(10):e76799.

Sarkar S, et al. Antidepressant pretreatment for the prevention of interferon alfa-associated depression: a systematic review and meta-analysis. *Psychosomatics*. 2013 Sep 4. pii: S0033-3182(13)00130-8.

Rowan P. Does prophylactic antidepressant treatment boost interferon-alpha treatment completion in HCV? *World J Virol.* 2013 Nov 12;2(4):139-45.

J & J Fined For False Marketing

According to the U.S. Department of Justice, J&J's Janssen unit pleaded guilty to charges of misbranding and filing false claims for their drug Risperdal® and agreed to pay fines that it improperly promoted Risperdal® to the elderly, children, and people with developmental disabilities while paying doctors and pharmacies kickbacks for prescriptions. The $2.2 billion settlement, the government's third-largest with a pharmaceutical company and the result of whistle-blower suits, includes $1.6 billion in civil payments to the U.S. and 45 states for Risperdal,® Invega®, and a cardiac medication, Natrecor.®

Arizona's Controlled Substance Monitoring Program (CSPMP)

Effective December 21, 2013, the CSPMP began service by Optimum Technology. The rules and regulations will not change. It will continue to be a program designed to provide information regarding the prescription of controlled substances in order to prevent the improper or illegal use of controlled substances and shall not infringe on the legitimate prescribing of a controlled substance by a pre-scribing practitioner acting in good faith and in the course of professional practice. The new website address is https://www.azrxreporting.com/

New providers can find registration information at www.azpharmacy.gov/pmp/default.asp For technical support, Optimum Technology can be reached at 1-866-683-2476 or azrxreporting@otech.com

Lawsuit Filed In 1981 Is Settled

After more than three decades of court monitors, negotiations, and funding swings, a lawsuit over how the State of Arizona cares for its seriously mentally ill (SMI) residents was settled on January 8, 2014. The lawsuit, Arnold vs. Sarn, was filed in 1981 when advocates for the SMI living in Maricopa County, Arizona, turned to the courts for relief in treating patients who did not qualify for Medicaid. The settlement covers nearly 19,000 SMI residents of Maricopa County. Reported is that the services the agreement outlined will also extend to mental health patients in Arizona's 14 other counties.