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Celecoxib as Adjunctive Treatment in Acute Mania

REVIEW OF: Mousavi SY, Khezri R, Karkhaneh-Yousefi MA, et al. A randomized, double-blind placebo-controlled trial on effectiveness and safety of celecoxib adjunctive therapy in adolescents with acute bipolar mania. *J Child Adolesc Psychopharmacol*. 2017;27(6):494–500. doi:10.1089/cap.2016.0207.

STUDY TYPE: Randomized, double-blind, placebo-controlled trial

Emotional stress can trigger an inflammatory cascade response and increase blood levels of proinflammatory cytokines—including IL-1, IL-6, and tumor necrosis factor (TNF-α). These same inflammatory markers intensify in acute episodes of depression and mania. So, would blocking the inflammatory cascade aid in treating acute episodes of mood disorders?

Celecoxib works by selective inhibition of cyclooxygenase-2 and reducing prostaglandin synthesis. The authors of this research previously demonstrated positive benefit during trials of celecoxib as an adjunctive treatment in adults with acute bipolar mania, obsessive compulsive disorder, and depression. This study explores the safety and efficacy of celecoxib in treating acute mania in adolescents.

This study was an 8-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted at an inpatient psychiatric hospital with 40 adolescents (ages 12–17). The subjects met criteria for a moderate to severe episode of bipolar mania without psychosis. In the treatment protocol, all adolescents received treatment with lithium (target blood level of 0.8–1.1) and risperidone (1 mg per day, then increasing to 3 mg per day). The treatment group also received celecoxib (100 mg twice daily), while the control group received a placebo over an 8-week period. Treatment started in the hospital setting, then continued in an outpatient clinic when the patients were ready for discharge.

RESULTS

The primary outcome was change in the Young Mania Rating Scale (YMRS), measured at baseline and at weeks 2, 4, and 8. At week 8, there was a significant difference in the change in YMRS scores between the celecoxib and control groups ($p = 0.04$). A secondary outcome measured was the Clinical Global Impressions—Improvement (CGI-I) scale: There was a trend in favor of the celecoxib group that did not reach significance ($p = 0.09$). For the safety analysis, the most common adverse events reported were increased appetite and dry mouth, but there were no significant differences between the groups in any of the reported adverse events. Cardiovascular health was also monitored by physical exam and electrocardiogram, and no patient experienced a cardiovascular event during the study.

THE CARLAT TAKE

Reducing the inflammatory cascade as part of the treatment for mood disorders is garnering more traction in the mental health community. This study is another mark in the positive

column, particularly for celecoxib. Other anti-inflammatory medications are also being looked at, including the statins and N-acetylcysteine.

PRACTICE IMPLICATIONS

While the idea of reducing inflammation as part of the treatment regimen for a manic episode shows promise, more research is necessary before recommending use of celecoxib. The data show that celecoxib may be helpful in the acute treatment of a mood episode, but how long should treatment last? Should we follow blood levels of inflammatory markers to guide treatment? What are the risks of longer-term treatment? More studies are needed to answer these questions.

Which Are the Most Dangerous Antidepressants?

REVIEW OF: Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. poison control centers, 2000–2014. *Am J Psychiatry*. 2017;174(5):438–450. doi:10.1176/appi.ajp.2016.16050523.

STUDY TYPE: Retrospective cohort study

We often prescribe antidepressants to patients who are suicidal, and unfortunately, some people use these very medications to try to kill themselves. It's been known for some time that tricyclic antidepressants are among the most toxic in overdose, so we embraced the SSRIs and later medications in part because they are considered to be safer. But how safe are they? A new study attempts to answer that question.

Researchers identified all 48 FDA-approved medications likely to be prescribed for depression, and then searched for these drugs in the National Poison Data System, which lists all reports of poisoning in the U.S. There were more than 950,000 poisoning reports involving these medicines from 2000 through 2014.

The hazard level of the drugs was measured in two ways: a morbidity index, which described the proportion of exposures that led to an injury serious enough to require hospitalization (like an ICU admission for cardiac monitoring after a tricyclic ingestion); and a mortality index, which is the proportion of exposures that led to death. The people involved in these events had a mean age of 35.8 years, and 62.8% were female.

RESULTS

This study reports a cornucopia of interesting results, and there's no way to cover them all in this synopsis. Here are some of the highlights that we found especially clinically relevant.

1. The two most dangerous drugs of all 48 studied were the tricyclic amitriptyline (morbidity index of 345/1,000 and mortality index of 3.8/1,000) and lithium (325/1,000 and 1.3/1,000).
2. Not surprisingly, tricyclics and MAOIs as classes had the highest morbidity and mortality rates.
3. Clomipramine was the safest of all tricyclics and had overdose indexes similar to drugs like citalopram and mirtazapine.
4. The "second generation" antidepressants were generally much safer than tricyclics and MAOIs (these included SSRIs, SNRIs, and others such as bupropion and mirtazapine). Within this group of safer drugs, here were some outliers:
   - Bupropion and venlafaxine were ranked #1 and #2 respectively in highest mortality rates among the second-generation antidepressants; bupropion had the highest morbidity rate.

- Among the SSRIs, citalopram was the most dangerous, and in one comparison, it was 4 times more likely to be fatal than sertraline and escitalopram.

5. Among atypical antipsychotics, olanzapine and quetiapine had the highest morbidity rates, with respiratory depression being a particularly common problem with these agents.

THE CARLAT TAKE

Before making wholesale changes in your prescribing habits, you should step back and realize how uncommon these bad events actually are. For example, bupropion, the "most lethal" of the second-generation antidepressants, led to 47 deaths out of over 62,000 overdoses over 15 years. The chance that one of your patients will OD on bupropion is already very scant, and then, among those rare overdose victims, less than 1 person out of 1,000 will die.

PRACTICE IMPLICATIONS

Nonetheless, there are a lot of thought-provoking data points in this paper that might affect our practices. If you're deciding between amitriptyline and duloxetine for fibromyalgia, go with the much safer duloxetine. Bupropion and venlafaxine are the most likely to be hazardous among the newer antidepressants—which is unfortunate, since bupropion is on the list of first-line antidepressants for many clinicians. Citalopram really is more dangerous than its racemic cousin escitalopram, meaning that the FDA warning about citalopram dosing is sounding more reasonable than before.

The bottom line is that you should add these data to the many other factors you consider in deciding which antidepressant to prescribe. And don't forget the basics, such as limiting refills to a weekly supply in patients at high risk of overdosing.