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## Off-Label Atypical Use: Few Benefits, Serious Adverse Effects

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September 27, 2011 – Off-label use of atypical antipsychotics may do more harm than good, a new meta-analysis suggests.

A combined analysis of more than 150 efficacy trials showed significant increases in behavioral symptom scores for dementia in the elderly after they were treated with aripiprazole, olanzapine, or risperidone; benefits for nonelderly patients with generalized anxiety disorder (GAD) after they received quetiapine; and benefits for patients with obsessive-compulsive disorder (OCD) after receiving risperidone augmentation.

However, analysis of more than 200 adverse outcome studies showed that treatment-related adverse events, including death, were common in these patient groups.



**Dr. Alicia Ruelaz  
Maher**

"Besides the small but statistically significant effect found for dementia, the other improvements were a bit smaller than we expected, with moderate effects for GAD and OCD," lead author Alicia Ruelaz Maher, MD, psychiatrist at the Akasha Center for Integrative Medicine in Santa Monica, California, and assistant clinical professor in psychiatry at the University of California, Los Angeles, School of Medicine, told *Medscape Medical News*.

"As for the other conditions that these medications commonly treat, we just did not find enough of an effect. And despite olanzapine being known to cause weight gain, I was surprised to find it was not effective in causing weight gain in eating disorders," said Dr. Maher, who is also a clinical adjunct at the RAND Health Southern California Evidence-Based Practice Center in Santa Monica.

She noted that the study is the "largest study of its kind on this subject," and prompted clinicians to reconsider the way they prescribe atypical antipsychotics.

"I think the biggest takeaway is that instead of just prescribing blindly, we now have evidence to guide us. There are certainly times when the cost-benefit analysis would go towards using medication, but I would hope that the side effects are kept in mind."

The [study appears](#) in the September 28 issue of *JAMA*.

### Doubling of Off-Label Use

"Atypical antipsychotic medications are approved for marketing and labeling by the US Food and Drug Administration (FDA) for treating schizophrenia, bipolar disorder, and depression under drug-specific circumstances," write the researchers.

However, these medications "are commonly used" off-label to treat dementia, anxiety, OCD, eating disorders, substance abuse, and posttraumatic stress disorder.

"We've been noticing that off-label use is increasing. In fact, over the past several years it has doubled," said Dr. Maher.

"Some clinicians feel that if a medication is effective in treating 1 condition, it might also be effective in treating others. And that often works, especially in psychiatry. However, there are also plenty of instances where off-label use was determined to be useless or even harmful."

To evaluate the benefits and safety of these medications for off-label use, the investigators examined data from 162 trials with efficacy outcomes conducted through May 2011.

"Controlled trials comparing an atypical antipsychotic medication (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, or paliperidone) with placebo, another atypical antipsychotic medication, or other pharmacotherapy for adult off-label conditions were included," report the researchers.

"Clozapine was excluded due its almost exclusive use for schizophrenia," they add.

### **Minimal Efficacy**

A total of 231 large observational studies were also examined that assessed adverse events and included at least 1000 patients each.

The efficacy review included 14 placebo-controlled trials that evaluated elderly patients with dementia who had symptoms such as psychosis, mood alterations, and aggression.

Overall results showed that aripiprazole, olanzapine, and risperidone showed small but significant effect changes, ranging from 0.12 to 0.20. Quetiapine showed an effect change of 0.11, but this was not deemed significant.

There was a difference of 3.41 points in the pooled Neuropsychiatric Inventory total score for dementia behavior symptoms between treatment with antipsychotics and with placebo. However, this was below the 4-point improvement threshold "considered to be the minimum clinically observable change," report the researchers.

In combined analysis of trials evaluating GAD, a "favorable response" was defined as showing at least 50% improvement on the Hamilton Anxiety Rating Scale. Overall results showed that quetiapine was associated with a 26% greater likelihood of a favorable response at 8 weeks than placebo.

Augmentation with risperidone after not responding to other treatments was associated with a 3.9-fold greater likelihood than placebo of a favorable response (showing at least a 25% improvement on the Yale-Brown Obsessive Compulsive Scale) for patients with OCD.

The study authors note that "evidence does not support" using olanzapine to treat eating disorders, or using any antipsychotic medications to treat substance abuse. Furthermore, they add, "[t]he level of evidence is mixed regarding personality disorders and is moderate for an association of risperidone with improving [posttraumatic stress disorder]."

### **Rethinking Off-Label Use**

Adverse events in elderly patients included an increased risk for death (pooled odds ratio, 1.54) and urinary tract symptoms overall, stroke for risperidone, and extrapyramidal symptoms for olanzapine and risperidone compared with placebo.

In the nonelderly, treatment-related adverse effects from antipsychotics included weight gain (especially with olanzapine), extrapyramidal symptoms, fatigue, sedation, and akathisia for aripiprazole.

"This systematic review demonstrates evidence for the efficacy of atypical antipsychotic medications for only a few of the off-label conditions that are currently being treated," write the researchers.

"This evidence should prove useful for clinicians considering off-label prescribing...and should contribute to optimal treatment decision-making for individual patients with specific clinical symptoms and unique risk profiles."

Dr. Maher added that she hopes this leads to clinicians examining each patient's individual needs.

"For example, if a patient already has kidney problems, then urinary tract symptoms might be a bigger issue than in someone who doesn't. It's just really about looking at the individual."

However, she also noted that although moderate levels of evidence were found for some of these conditions, further research might bring about changes in the results.

"We need to use this information and be wary of prescribing when it isn't warranted; but also we need to keep looking at this issue in future studies."

### A Complicated Decision



**Dr. Anthony  
Rothschild**

"While meta-analysis studies are always useful, one doesn't make treatment decisions based on just 1 [study]," Anthony Rothschild, MD, Irving and Betty Brudnick endowed chair and professor of psychiatry at the University of Massachusetts Medical School in Worcester, and director of the Center for Psychopharmacologic Research and Treatment, told *Medscape Medical News*.

"Overall, there were some new, interesting things. And their findings that some of the newer, atypical antipsychotics helped with behavioral symptoms in dementia, [GAD], and augmentation in [OCD] is all useful information," said Dr. Rothschild.

He noted that although the investigators' report of adverse events and risks with these medications was also helpful, it really comes down to what a clinician thinks is right.

"The clinician with a patient in their office has to weigh the benefits vs the risks for that individual person. For example, the investigators found a small but significant benefit in symptoms of dementia for some of the medications. But that was coupled with a small but significant increased risk of death. So clinicians have to make a judgment, and it's a complicated decision."

Dr. Rothschild said it was interesting that the analysis did not find any therapeutic benefit for using olanzapine in eating disorders, or any of the atypicals for substance abuse.

In addition, he voiced concerns that the investigators did not include studies that examined these medications for patients with psychotic depression, which commonly involves delusions.

"It's quite a prevalent condition; epidemiologic studies show 15% to 18% of people with depression have this form of it. But it's not even discussed in this article, which is curious because all treatment of it is off-label. There is currently no medication or medication combination that has FDA approval for treating it, but other studies have written that atypical antipsychotics are useful in combination with an antidepressant. It would have been nice if [these investigators] had included a paragraph or 2 on this debilitating disorder."

He noted that the question of why certain studies were included and others were not is an issue with any meta-analysis.

"That's why you wouldn't just hang your practice on 1 article. You have to take the totality of all the evidence. And I'd say a study like this adds to our knowledge base when it comes to making that complicated risk-benefit analysis," concludes Dr. Rothschild.

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*support from the National Institute of Mental Health, Cyberonics, Takeda, and St. Jude; and having served as a consultant to Dey Pharma, Eisai Medical, GlaxoSmithKline, Eli Lilly, Noven Pharmaceuticals, Pfizer, and Shire Pharmaceuticals. However, he said that of these relationships, only the National Institutes of Health grant was in the area of antipsychotics. He also receives royalties from American Psychiatric Press for several of his books, including The Evidence-Based Guide to Antipsychotic Medications.*

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