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Current Findings in the Off-Label Use of Atypical Antipsychotics

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A class of medications once reserved for the most serious of mental illnesses, the atypical antipsychotic medications, has become routinely prescribed in primary care offices for the treatment of delirium, depression, autism, dementia, and other disorders. The treatment of many of these conditions with atypical antipsychotics is not approved by the FDA and the evidence base for their off-label use is often in question. In fact, 54% of all office visits associated with the prescription of an atypical antipsychotic involves off-label use.[1] Atypical antipsychotics are the fifth most expensive medication class in the U.S. In 2010, spending was $16.1 billion (aripiprazole $4.6 billion; quetiapine $4.4 billion; olanzapine $3.0 billion).[2] Because they have been associated with a lower incidence of extrapyramidal adverse effects, atypical antipsychotics have largely replaced traditional antipsychotics. As experience with the atypical agents accrues, however, serious and distinct adverse effects with atypicals have emerged.[1] Atypical antipsychotics can cause weight gain and lead to a higher risk of other metabolic abnormalities (e.g. diabetes) compared to the older, traditional antipsychotics.[3] Also, current comparative evidence (based on their indicated use for the treatment of schizophrenia) suggests no definitive differences in efficacy or net adverse effect profiles between the two drug classes.[4]

Patterns of Use

A recent study by Alexander, et al[1] evaluated the patterns of antipsychotic use in the outpatient setting and found that from 1995 to 2008 the use of atypical agents expanded for bipolar disorder (10 to 34%), remained stable for depression (12 to 14%), and declined for schizophrenia (56 to 23%). The authors concluded that atypical use has grown far beyond substitution for the infrequently used typical agents. Growth in use was seen in all age categories. They found that antipsychotic use for indications without FDA approval increased from 4.4 million visits in 1995 to 9.0 million in 2008 with an estimated cost associated with off-label use in 2008 of $6.0 billion. While the use of atypicals for the treatment of schizophrenia declined, their use in bipolar affective disorder, attention deficit hyperactivity disorder/conduct disorder, and anxiety all increased.

Agency for Healthcare Research and Quality Report

Not all off-label use is inappropriate. There is a growing body of evidence to support the use of certain atypical antipsychotics for off-label indications. A recent report from the Agency for Healthcare Research and Quality (AHRQ)[5] included a review of the following off-label uses for atypical antipsychotics: anxiety, attention deficit disorder (ADHD), dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome. The following are key findings from the report:

Current trends:

- Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.
- One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. Use of atypicals in the elderly is much higher in long-term care settings than in the community.
- Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.
- At least 90% antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.

Summary of the Evidence:

Table 1. Efficacy for the following off-label indications and atypical antipsychotics	
Moderate to High Evidence	
Off-label Indication	Atypical Antipsychotic
Generalized anxiety disorder	Quetiapine
Dementia (overall)	Aripiprazole, risperidone
Dementia (psychosis)	Risperidone
Dementia (agitation)	Olanzapine, risperidone
Depression (SSRI/SRNI augmentation)	Aripiprazole (labeled indication), quetiapine (labeled use for quetiapine XR), risperidone
Depression (monotherapy)	Quetiapine
Obsessive Compulsive Disorder (SSRI augmentation)	Risperidone
PTSD	Risperidone

Table 2. Inefficacy for the following off-label indications and atypical antipsychotics	
Moderate to High Evidence	
Off-label Indication	Atypical Antipsychotic
Eating Disorders	Olanzapine
Substance Abuse (alcohol)	Aripiprazole
MDD (monotherapy)	Olanzapine

- Strength of evidence is low for the following off-label indications:
  - ADHD
  - Insomnia
  - Substance abuse (cocaine, methamphetamine, methadone)
  - Personality disorders
  - Tourette's syndrome
- There is almost no evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or medical comorbidities.
- In terms of adverse effects for the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event (see Table 3)

Table 3. Adverse Events Associated with the Off-Label Use of Atypical Antipsychotics[5]	
Adverse Event	Placebo Comparison
Weight Gain--Elderly	More common in patients taking olanzapine and risperidone
Weight Gain—Adults	More common in patients taking aripiprazole, olanzapine, quetiapine and risperidone
Weight Gain--Children	More common with risperidone; No difference with ziprasidone
Mortality—Elderly	Difference in risk for death is small, but statistically significant for atypical antipsychotics. No differences between drugs in class (no studies for ziprasidone in this population)
Endocrine/ Diabetes—Adults	More common with quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA—Elderly	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In the most recent meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
EPS	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Sedation—Adults	More common in patients taking aripiprazole, olanzapine, quetiapine, ziprasidone and quetiapine than placebo
Abbreviations: PCT=placebo controlled trial; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms	

- There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.
    - Most trials used flexible dosing, resulting in patients taking a wide range of doses.
    - According to the meta-analysis conducted by AHRQ, using the percentage of remitters and responders as identified by the MADRS as outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs.
    - More trials examining different doses of other atypicals for MDD are needed as are dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder.
- Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported follow-up time.

Summary

Recent evidence has demonstrated that the majority of atypical antipsychotic use is for off-label indications. The benefits and harms associated with atypical antipsychotics in off-label uses vary. For global behavioral symptom scores associated with dementia in elderly patients, small but statistically significant benefits have been observed for aripiprazole, olanzapine, and risperidone. Quetiapine has been associated with benefits in the treatment of generalized anxiety disorder, and risperidone is associated with benefits in the treatment of obsessive-compulsive disorder. Adverse effects, however, are common with each of these agents. The use of atypical antipsychotics, particularly for conditions that are considered off-label, requires a careful evaluation of their risks versus benefits. The benefits of using atypical antipsychotics should include clear and definable treatment goals especially if they are used in the place of other agents with demonstrated comparable or superior effectiveness

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