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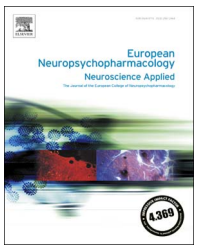

REVIEW

Benefits and harms of atypical antipsychotics for agitation in adults with dementia

Martin R. Farlow[a,1], **Tatyana A. Shamliyan**[b,*]

[a]*Department of Neurology, IU Alzheimer's Disease and Related Disorders, 355 W. 16th Street, Suite 4700, Indianapolis, IN 46202, USA*
[b]*Evidence-Based Medicine Quality Assurance, Elsevier, 1600 JFK Blvd 20th floor, Philadelphia, PA 19103, USA*

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Quetiapine

Abstract
We evaluated the most current evidence regarding the benefits and harms of atypical antipsychotics in adults with dementia.
In June 2016, following a protocol developed *a priori*, we systematically searched several databases for published and unpublished data from randomized controlled trials (RCT), observational studies, and meta-analyses; conducted direct meta-analyses using a random effects model; and graded the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.
One high-quality meta-analysis and published and unpublished data from 8 RCTs and 12 large observational studies met inclusion criteria. When compared with placebo, aripiprazole, risperidone, and olanzapine but not quetiapine result in modest (standardized mean difference <0.5 standard deviations) improvement in neuropsychiatric symptoms. Aripiprazole, risperidone, quetiapine, and olanzapine are associated with increased odds of acute myocardial infraction, and risperidone and olanzapine are associated with increased odds of hip fracture. Observational studies suggest no differences in all-cause mortality between atypical antipsychotics.
Observational studies suggest that atypical antipsychotics are associated with lower risk of all-cause mortality and extrapyramidal symptoms but higher risk of stroke when compared with conventional antipsychotics.

*Corresponding author.
E-mail addresses: ajperk@iu.edu (M.R. Farlow), t.shamliyan@elsevier.com (T.A. Shamliyan).
[1]Fax: +1 317 963 7533.

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To manage agitation in adults with progressive dementia, clinicians may recommend atypical antipsychotics with continuous monitoring of behavioral symptoms, informing patients and their families or caregivers of the significant risk of adverse effects and baseline risk of acute myocardial infraction and bone fractures.

1. Introduction

A growing proportion of adults globally have dementia with behavioral disturbances and corresponding burden on health, well-being, and societal costs (Reus et al., 2016). Conventional antipsychotic medications are associated with increased risk of serious adverse effects (Reus et al., 2016). Atypical antipsychotics are among the most commonly prescribed medications in outpatient settings and nursing homes, despite warnings from regulatory agencies about the potential harms of off-label use of these drugs specifically for elderly adults with dementia (Company, 2016; Company, 2015; Janssen Pharmaceuticals, 2016; Levinson, 2011; LP, 2016; Thompson Coon et al., 2014). For instance, the antipsychotic aripiprazole had sales of about $7.2 billion in 2015 (Brooks, 2015). Previous systematic reviews evaluated the short-term benefits and harms of off-label atypical antipsychotics in adults with dementia, focusing on randomized controlled trials (RCT) (Ballard et al., 2011; Gentile, 2010; Maglione et al., 2011). Individual observational studies suggested increased risk of mortality and morbidity associated with atypical antipsychotics (Langballe et al., 2014; Maust et al., 2015). This review focuses on the most current evidence from all available RCTs and observational studies that examined the benefits and harms of atypical antipsychotics in adults with dementia.

2. Experimental procedures

We developed a protocol (Appendix A) for a systematic literature review following recommendations from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (Higgins and Green, 2011; Slutsky et al., 2010).

We refined the clinical questions and defined the target population as patients diagnosed with dementia (Diagnostic and Statistical Manual of Mental Disorders [DSM] IV-V criteria) and agitation (Appendix A). Interventions eligible for this review investigated the role of atypical antipsychotics including risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, and paliperidone (Appendix A).

We conducted a comprehensive search in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov from 2010 to June 2016 to find published and unpublished meta-analyses, RCTs, and nationally representative controlled observational studies that reported adjusted effect estimates (strings are available in Appendix B) (Balshem et al., 2008). All of the authors and the medical librarian determined the studies' eligibility. All citations found during the searches are stored in a reference database.

An external contractor, DOC Data Software Platform v2.0 (Doctor Evidence LLC, Santa Monica, Calif.), performed dual abstraction and quality control of the data (Appendix C). We performed meta-analyses using random effects models of hypotheses, with the exact same definitions of the active and control intervention and patient outcomes, and similar follow-up time (Fu et al., 2011). We calculated absolute risk difference, number needed to treat, and number of attributable events based on data from the published RCTs, using STATA software. Statistical significance was evaluated at a 95% confidence level.

We evaluated the quality of systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) (Shea et al., 2009). For primary studies, we used the Cochrane risk of bias tool on a 3-point scale: high bias, low bias, and unclear (Higgins et al., 2011; Viswanathan et al., 2013). For clinical practice guidelines, we used the Appraisal of Guidelines Research & Evaluation (AGREE II; 2009) tool, which covers 23 items in 6 domains and 2 overall global ratings (Brouwers et al., 2010a, 2010b).

The authors assigned the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Appendix A) (Schünemann et al., 2013).

3. Results

Our team retrieved and screened 401 studies and included in this review 70 references (PRISMA diagram in Appendix A).

We identified 1 high-quality meta-analysis, published and unpublished data from 4 RCTs, and 5 large observational studies that compared atypical antipsychotics with placebo or no active treatments (De Deyn et al., 2012; Devanand et al., 2012; Huybrechts et al., 2012; Jalbert et al., 2011; Jalbert et al., 2010; Lin et al., 2014; Maust et al., 2015; Otsuka Pharmaceutical et al., 2010; Tan et al., 2015).

Primary small RCTs enrolled adults with dementia and behavioral disturbance (De Deyn et al., 2012; Devanand et al., 2012; Otsuka Pharmaceutical et al., 2010). Observational studies analyzed the association between mortality and morbidity and atypical antipsychotics in adults treated with these drugs regardless of specific diagnosis (Huybrechts et al., 2012; Jalbert et al., 2011; Jalbert et al., 2010; Lin et al., 2014; Maust et al., 2015). We included such studies with mixed populations because the adverse effects of atypical antipsychotics are likely the same regardless of the presence of dementia.

Moderate-quality evidence from RCTs suggests that aripiprazole improves neuropsychiatric symptoms at the expense of higher risk of cardiac arrest, bone fracture, constipation, extrapyramidal disorder, somnolence, and apathy when compared with placebo in adults with dementia and

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