Senior Minutes

Special Edition July 4th

Beyond Antipsychotic in Dementia and Alzheimers:
The Promise of Behavioral Intervention and Counseling

Atypical anitpsycotics' 'black box' warnings: What are the risks?

The FDA warned prescribers in 2003 of increased risk of "cerebrovascular adverse events including stroke" in dementia patients treated with risperidone vs placebo. Similar cerebrovascular warnings have been issued for olanzapine and aripiprazole. Although the absolute risk difference was generally 1% to 2% between antipsychotic and placebo-treated patients, the relative risk was approximately 2 times higher with antipsychotics because the prevalence of these events is low in both groups.3

Perhaps more daunting, after a meta-analysis of 17 trials using atypical antipsychotics in elderly patients with dementia-related psychosis, the FDA in 2005 issued a black-box warning of increased mortality risk with atypical antipsychotics (relative risk 1.6 to 1.7) vs placebo. The mortality rate in antipsychotic-treated patients was about 4.5%, compared with about 2.6% in the placebo group. Although causes of death varied, most were cardiovascular (heart failure, sudden death) or infectious (pneumonia). This warning was applied to atypical antipsychotics as a class. As with cerebrovascular risks, the absolute mortality risk difference was 1% to 2%.

References:
Summarized from: Current Psychiatry, June 2008, Vol. 7, No.6, Pages 52, 55, 57, 58, 64

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How well do psychosocial/behavioral therapies manage psychosis/agitation in dementia?

Treatment	Evidence/Results
Caregiver psychoeducation/support	Several positive RCTs (evidence grade A)
Music therapy	6 RCTs, generally positive in the short term (evidence grade B)
Cognitive stimulation therapy	Three-quarters of RCTs showed some benefi t (evidence grade B)
Snoezelen therapy (controlled multisensory stimulation)	3 RCTs with positive short-term benefi ts (evidence grade B)
Behavioral management therapies (by professionals)	Largest RCTs with some benefi ts (grade B)
Staff training/education	Several positive studies of fair-to-good methodologic quality (evidence grade B)
Reality orientation therapy	Best RCT showed no benefi t (evidence grade D)
Teaching caregivers behavioral management techniques	Overall inconsistent results (evidence grade D)
Simulated presence therapy	Only 1 RCT which was negative (evidence grade D)
Validation therapy	1-year RCT with mixed results (evidence grade D)
Reminiscence therapy	A few small studies with mixed methodologies (evidence grade D)
Therapeutic activity programs (such as excesise, puzzle play)	Varied methods and inconsistent results (evidence grade D)
Physical environmental stimulation (such as altered visual stimuli, mirrors, signs)	Generally poor methodology and inconsistent results; best results with obscuring exits to de creaseexit-seeking(evidence grade D)

Evidence grades from A (strongest) to D (weakest) were assigned in a review by Livingston G, Johnston K, Katona C, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 2005;162:1996-202
RCT: randomized controlled trial

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5-step evaluation of dementia patients with psychosis and/or agitation/aggression*

1. How dangerous is the situation?
- If the patient or others are at signifi cant risk and the patient does not respond quickly to behavioral strategies (such as verbal redirection/reassurance, stimulus reduction, or change of environment), consider acute pharmacotherapy. For instance, offer the patient an oral antipsychotic (possibly in dissolvable tablets) and then if necessary consider intramuscular olanzapine, aripiprazole, ziprasidone, haloperidol, or lorazepam
- For less acute situations, more thoroughly investigate symptom etiology and obtain informed consent before treatment

2. Establish a clear diagnosis/etiology for the symptoms
- Rule out causes of delirium (such as urinary tract infection, subdural hematoma, pneumonia) through appropriate physical examination and diagnostic studies
- Rule out iatrogenic causes, such as recent medication changes
- Rule out physical discomfort from arthritis pain, unrecognized fracture, constipation, or other causes
- Assess for potentially modifi able antecedents to symptom fl ares, such as seeing a certain person, increased noise, or social isolation
- Explore other common causes of behavioral disturbances, including depression, anxiety, and insomnia

3. Establish symptom severity and frequency, including:
- Impact on patient quality of life
- Impact on caregiver quality of life
- Instances in which the safety of the patient or others has been jeopardized
- Clear descriptions of prototypical examples of symptoms

4. Explore past treatments/caregiver strategies used to address the symptoms and their success and/or problematic outcomes

5. Discuss with the patient/decision-maker what is and is not known about possible risks and benefits of pharmacologic and nonpharmacologic treatments for psychosis and agitation/aggression in dementia

Source: Reference 5

* Agitation is defi ned as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual

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Typical antipsychotics: Safer than atypicals for older patients?

Study	Population	Summarized Results
Mortality		
Nasrallah et al	VA patients age ≥65 taking haloperidol or an atypical antipsychotic (n=1,553)	Approximately 4 times higher rate of death in those receiving haloperidol compared with those receiving atypicals
Wang et al	Pennsylvania adults age ≥65 with prescription coverage taking antipsychotics (n=22,890)	Typicals had higher relative risk (RR) of death at all time points over 180 days (RR 1.27 to 1.56), both in persons with and without dementia; higher risk associated with increased typical doses
Gill et al	Canadians age >65 with dementia (n=27,259 matched pairs)	Mortality rate was higher for users of typical vs atypical antipsychotics (RR 1.26 to 1.55)
Kales et al11	VA patients age >65 prescribed psychotropics after a dementia diagnosis (n=10,615)	Risk of death similar for atypical and typical antipsychotics
Schneeweiss et al	Cancer-free Canadians age ≥65 taking antipsychotics (n=37,241)	Higher mortality rates for those taking typical antipsychotics than those taking atypicals (RR 1.47); higher mortality associated with higher typical doses
Trifirò et al9	Adults age >65 with dementia receiving antipsychotics in Italy (n=2,385)	Equivalent rates of mortality in those taking typical and atypical antipsychotics
Stroke		
Gill et al	Canadians age ≥65 with dementia receiving antipsychotics (n=32,710)	Equivalent rates of ischemic stroke in those taking atypical and typical agents compared with those receiving atypicals
Liperoti et al	Nursing home residents with dementia hospitalized for stroke or TIA and matched controls (n=4,788)	Rates of cerebrovascular adverse events equivalent between users of atypical and typical antipsychotics

VA: Veterans Affairs; TIA: transient ischemic attack

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Pharmacologic alternatives to antipsychotics: What the evidence says

Treatment	Evidence/Results
Selective serotonin reuptake inhibitors	2 positive studies with citalopram (more effective than placebo for agitation in 1 trial and equivalent to risperidone for psychosis and agitation with greater tolerability in the other); 2 negative trials with sertraline
Other antidepressants	1 study showed trazodone was equivalent to haloperidol for agitation, with greater tolerability; another found trazodone was no different from placebo; other agents have only case reports or open-label trials
Anticonvulsants	3 trials showed divalproex was equivalent to placebo; 2 positive trials for carbamazepine, but tolerability problems in both; other agents tried only in case reports or open-label trials
Benzodiazepines/anxiolytics	3 trials showed oxazepam, alprazolam, diphenhydramine, and buspirone were equivalent to haloperidol in effects on agitation, but none used a placebo control; trials had problematic methodologies and indicated cognitive worsening with some agents (especially diphenhydramine
Cognitive enhancers	Some evidence of modest benefi t in mostly post-hoc data analyses in trials designed to assess cognitive variables and often among participants with overall mild psychiatric symptoms; prospective studies of rivastigmine and donepezil specifi cally designed to assess neuropsychiatric symptoms have found no difference compared with placebo
Miscellaneous drugs	Failed trial of transdermal estrogen in men; small study showed propranolol (average dose 106 mg/d) more effective than placebo

Source: References 5,21

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