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February 2009

Vol. 11, No. 2

Our Mission: Helping to prepare Iowa's health practitioners to care for our growing population of elders. *E-NEWS* is one of our methods of teaching through technology.

Each month, *E-NEWS* delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month's *E-NEWS* focuses on PHARMACOLOGIC MANAGEMENT OF BEHAVIORS IN DEMENTIA.

PHARMACOLOGIC MANAGEMENT OF BEHAVIORS IN DEMENTIA

In this issue of the *E-NEWS*, you will find abstracts for:

- A study that seeks to determine if manifestations of agitation show different degrees of response to divalproex sodium alone or in combination with second-generation antipsychotic agents.
 - An article that discusses alternatives to atypical antipsychotics for the management of dementia-related agitation.
 - A study that compares citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia.
 - An article that addresses managing risk when considering the use of atypical antipsychotics for older adults with dementia-related psychosis.
 - An article that presents a consensus statement on treatment options, clinical trials methodology, and policy for older adults with dementia-related symptoms of severe agitation and aggression.
 - A study that investigates the course of psychiatric and behavioral symptoms and the associated use of psychotropic medication in nursing home residents with dementia.
 - A study that examines clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease.
 - A study that evaluates the efficacy and safety of memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease.
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- Forester B, Vanelli M, Hyde J, Perez R, Ahokpossi C, Sribney W, Adkison L. Report on an open-label prospective study of divalproex sodium for the behavioral and psychological symptoms of dementia as monotherapy and in combination with second-generation antipsychotic medication. *Am J Geriatr Pharmacother.* 2007 Sep;5(3):209-17.

BACKGROUND: Studies of pharmacotherapy for agitation in dementia have primarily been limited to single-drug trials and have not determined if some forms of agitated behaviors are more responsive to treatment than others. OBJECTIVE: The goal of this study was to determine if manifestations of agitation (ie, physical aggression, physically nonaggressive behavior, and verbally agitated behaviors) show different degrees of response to divalproex sodium (extended release or sprinkles) alone or in combination with second-generation antipsychotic agents. METHODS: This was a 6-week, open-label, naturalistic pilot study of patients aged >60 years recruited from a geriatric psychiatry inpatient unit, 2 nursing homes, and 4 assisted living residences. Patients were referred for study if they displayed Behavioral and Psychological Symptoms of Dementia. The primary outcome measure was the Cohen-Mansfield Agitation Inventory (CMAI), an instrument whose subscales allow measurement of physically aggressive behaviors, physically nonaggressive behaviors (eg, wandering), and verbally agitated behaviors. The Neuropsychiatric Inventory-Nursing Home version (NPI-NH) was also used to assess patients' behavior. RESULTS: Fifteen patients were included in the study (10 men, 5 women; mean [SD] age, 81.9 [7.7] years). Total CMAI improved by 17.1% at week 1, showed an additional improvement of 3.4% at week 3, and no further improvement by week 6 (total score dropped by 1.1%). Aggressive behavior improved at weeks 3 and 6 while physically nonaggressive and verbally agitated behaviors improved at weeks 1 and 3, and lost much of the gains by week 6. The NPI-NH agitation/aggression score decreased a mean (SE) of 1.3 (0.5) points ($P = 0.03$), the irritability/lability subscale decreased a mean (SE) of 2.3 (0.6) points ($P = 0.005$), and the disinhibition subscale decreased a mean (SE) of 1.4 (0.4) points ($P < 0.01$). Seven patients were on divalproex monotherapy and 8 patients were on combination therapy. Daily doses of divalproex (mean dose, 656 mg/d) in combination with a second-generation antipsychotic were 28% lower than divalproex monotherapy (mean dose, 914 mg/d). The most common adverse events were somnolence (7 of 15) and gait disturbance (5 of 15). One death was observed in the study; the death was due to a prior medical condition and was judged unlikely to be study related. CONCLUSIONS: Patients with higher levels of agitation receiving divalproex had reduced agitation on the physical aggression subscale of the CMAI. Divalproex was less effective on physically nonaggressive behavior and verbal agitation. Irritability, as measured on the NPI-NH, was also reduced. Patients who received both divalproex and an antipsychotic agent were responsive at lower doses of divalproex. In either case, the effective dosage of divalproex was lower than that commonly used for epilepsy or mania in elderly patients. The most common adverse events included somnolence and gait disturbance.



- Passmore MJ, Gardner DM, Polak Y, Rabheru K. Alternatives to atypical antipsychotics for the management of dementia-related agitation. *Drugs Aging.* 2008;25(5):381-98.

Numerous recent studies have challenged the widely held belief that atypical antipsychotics are safe and effective options for the treatment of behavioural problems such as agitation in patients with dementia. Accordingly, there is a need to reconsider the place of atypical antipsychotics in the treatment of patients with dementia. The present article is intended to assist clinicians with the assessment and pharmacological management of agitation in patients with dementia. We review the risk-benefit evidence for the use of atypical antipsychotics in patients with dementia-related agitation (DRA). Emerging evidence indicates that, for patients with dementia, the risks associated with atypical antipsychotics may outweigh the benefits except for patients with severe agitation who require short-term chemical restraint. We then discuss the importance of a careful assessment to rule out potentially reversible factors contributing to DRA. Finally, we summarize the evidence supporting the use of medications other than antipsychotics to treat DRA. There is wide variability in the levels of evidence supporting the use of non-antipsychotic medication for the treatment of DRA. The best evidence currently exists for cholinesterase inhibitors and serotonin-specific reuptake inhibitor antidepressants. Emerging reports suggest that numerous other medications, for example, antiepileptics, lithium, anxiolytics, analgesics, beta-adrenoceptor antagonists, cannabinoid receptor agonists and hormonal agents, may prove to be viable alternatives to antipsychotics for the treatment of severe DRA and more research is urgently needed to help assess the effectiveness of these agents. A comprehensive biopsychosocial assessment and treatment plan is likely the most effective way to manage DRA.



- Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, Huber KA. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. *Am J Geriatr Psychiatry*. 2007 Nov;15(11):942-52.

OBJECTIVE: To compare citalopram and risperidone for the treatment of psychotic symptoms and agitation associated with dementia, with a priori hypotheses that risperidone would be more efficacious for psychosis and citalopram for agitation. METHODS: A 12-week randomized, controlled trial in nondepressed patients with dementia hospitalized because of behavioral symptoms (N = 103) was conducted at the University of Pittsburgh Medical Center. Participants were consecutively recruited on an inpatient unit if they had at least one moderate to severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions). Once they improved sufficiently, they were discharged to nursing homes, personal care homes, or residential homes for continued treatment. Planned pre-post and mixed model analyses of the main outcome measures of Neurobehavioral Rating Scale and Side Effect Rating Scale at baseline and at weekly/biweekly intervals were conducted. RESULTS: Completion rates did not differ for citalopram and risperidone (overall completion rate: 44%). Agitation symptoms (aggression, agitation, or hostility) and psychotic symptoms (suspiciousness, hallucinations, or delusions) decreased in both treatment groups but the improvement did not differ significantly between the two groups. There was a significant increase in side effect burden with risperidone but not with citalopram such that the two groups differed significantly. CONCLUSION: No statistical difference was found in the efficacy of citalopram and risperidone for the treatment of either agitation or psychotic symptoms in patients with dementia. These findings need to be replicated before citalopram or other serotonergic antidepressants can be recommended as alternatives to antipsychotics for the treatment of agitation or psychotic symptoms associated with dementia.



- Recupero PR, Rainey SE. Managing risk when considering the use of atypical antipsychotics for elderly patients with dementia-related psychosis. *J Psychiatr Pract*. 2007 May;13(3):143-52.

In 2005, responding to several studies, the FDA issued a black box warning on atypical (second generation) antipsychotic medications, noting that the drugs may increase the risk of cerebrovascular adverse events in elderly patients with dementia-related behavior disturbances. The black box warning has raised concern for clinicians, among whom atypical antipsychotics have gained favor for having a more tolerable side-effect profile than many other pharmacological treatment options. Complicating this concern are studies suggesting that other medications may have similar risks and a dearth of unbiased head-to-head studies comparing different treatment options. To effectively manage risk when treating elderly patients with dementia-related psychosis, physicians, patients, and caregivers must consider both acute risks (such as danger of bodily harm to the patient and others) and long-term risks (such as placement in a restrictive nursing home). If an atypical antipsychotic is chosen, additional risk management may be warranted. This paper presents a brief overview of relevant concerns and suggests some techniques to help minimize and manage risk, such as increased monitoring, informed consent, and thorough documentation. A sample clinical risk management form and a sample letter to the primary care physician are provided to help guide clinicians in improving their risk management practices when working with elderly patients suffering from dementia-related psychosis and related behavioral difficulties.



- Salzman C, Jeste DV, Meyer RE, Cohen-Mansfield J, Cummings J, Grossberg GT, Jarvik L, Kraemer HC, Lebowitz BD, Maslow K, Pollock BG, Raskind M, Schultz SK, Wang P, Zito JM, Zubenko GS. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry*. 2008 Jun;69(6):889-98.

OBJECTIVE: Atypical antipsychotic drugs have been used off label in clinical practice for treatment of serious dementia-associated agitation and aggression. Following reports of cerebrovascular adverse events associated with the use of atypical antipsychotics in elderly patients with dementia, the U.S. Food and Drug Administration (FDA) issued black box warnings for several atypical antipsychotics titled "Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia." Subsequently, the FDA initiated a metaanalysis of safety data from 17 registration trials across 6 antipsychotic drugs (5 atypical antipsychotics and haloperidol). In 2005, the FDA issued a black box warning regarding increased risk of mortality associated

with the use of atypical antipsychotic drugs in this patient population. PARTICIPANTS: Geriatric mental health experts participating in a 2006 consensus conference (Bethesda, Md., June 28-29) reviewed evidence on the safety and efficacy of antipsychotics, as well as nonpharmacologic approaches, in treating dementia-related symptoms of agitation and aggression. EVIDENCE/CONSENSUS PROCESS: The participants concluded that, while problems in clinical trial designs may have been one of the contributors to the failure to find a signal of drug efficacy, the findings related to drug safety should be taken seriously by clinicians in assessing the potential risks and benefits of treatment in a frail population, and in advising families about treatment. Information provided to patients and family members should be documented in the patient's chart. Drugs should be used only when nonpharmacologic approaches have failed to adequately control behavioral disruption. Participants also agreed that there is a need for an FDA-approved medication for the treatment of severe, persistent, or recurrent dementia-related symptoms of agitation and aggression (even in the absence of psychosis) that are unresponsive to nonpharmacologic intervention. CONCLUSIONS: This article outlines methodological enhancements to better evaluate treatment approaches in future registration trials and provides an algorithm for improving the treatment of these patients in nursing home and non-nursing home settings.



- Selbaek G, Kirkevold Ø, Engedal K. The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes--a 12-month follow-up study. *Am J Geriatr Psychiatry*. 2008 Jul;16(7):528-36.

OBJECTIVE: This study investigates the natural course of neuropsychiatric symptoms and the concomitant use of psychotropic medication among a large and representative sample of nursing-home patients with dementia. METHOD: The authors performed two data collections with structured interviews in a 1-year follow-up cohort-study including 26 nursing homes in four counties in two Norwegian health regions. The main outcome measures were baseline and follow-up frequencies, persistence and incidence of neuropsychiatric symptoms, and the change in neuropsychiatric symptoms with regard to the use of psychotropic medication. RESULTS: At baseline a representative sample of 1,163 nursing-home patients participated, of whom 933 had dementia. At the follow-up interview after 1 year, 633 of the patients who had dementia at baseline were assessed. Clinically significant neuropsychiatric symptoms were exhibited by 84% of patients with dementia at the baseline or follow-up interviews. Overall persistence of symptoms was 79%. Individual symptoms, such as depression (58%), delusions (56%), and agitation/aggression (47%) had resolved at a high rate. Persistent use of antidepressants (79%), antipsychotics (75%), or any psychotropic drug (88%) was common. There were no differences between users and nonusers of antipsychotics or antidepressants regarding the course of psychosis, agitation, or depression over the 1-year observation period. CONCLUSION: Neuropsychiatric symptoms are ubiquitous in nursing home patients with dementia. Overall the symptoms are chronically present, whereas individual symptoms often show an intermittent course. Long-term use of psychotropic medication is extensive. Uncertainty about treatment effects emphasizes the need for further treatment trials.



- Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Lieberman JA, Schneider LS; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry*. 2008 Jul;165(7):844-54.

OBJECTIVE: The study measured the effects of atypical antipsychotics on psychiatric and behavioral symptoms in patients with Alzheimer's disease and psychosis or agitated behavior. METHOD: The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) Alzheimer's disease effectiveness study included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior. Patients were assigned randomly to masked, flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. Patients could be randomly reassigned to a different medication at the clinician's discretion, which ended phase 1. Psychiatric and behavioral symptoms, functioning, cognition, care needs, and quality of life were measured at regular intervals. RESULTS: In relation to placebo, the last observation in phase 1 showed greater improvement with olanzapine or risperidone on the Neuropsychiatric Inventory total score, risperidone on the Clinical Global Impression of Changes, olanzapine and risperidone on the Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor, and risperidone on the BPRS psychosis factor. There was worsening with olanzapine on the BPRS withdrawn depression factor. Among

patients continuing phase 1 treatment at 12 weeks, there were no significant differences between antipsychotics and placebo on cognition, functioning, care needs, or quality of life, except for worsened functioning with olanzapine compared to placebo. CONCLUSION: In this descriptive analysis of outpatients with Alzheimer's disease in usual care settings, some clinical symptoms improved with atypical antipsychotics. Antipsychotics may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. They do not appear to improve functioning, care needs, or quality of life.

- Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry*. 2008 Mar;69(3):341-8.

OBJECTIVE: Long-standing evidence indicates that Alzheimer's disease patients with behavioral symptoms have a worse prognosis and a more rapid disease progression. The current retrospective analysis evaluated the efficacy and safety of memantine in a subpopulation of patients with Alzheimer's disease exhibiting behavioral symptoms of agitation/aggression or psychosis at baseline. METHOD: A pooled analysis was conducted in people with agitation/aggression or psychosis from 3 large 6-month, randomized studies in moderately severe to severe Alzheimer's disease. The effect of memantine and placebo on these specific symptoms was evaluated using the Neuropsychiatric Inventory (NPI) subitem cluster of agitation and psychosis. Outcomes on global, cognitive, and functional measures were also analyzed. RESULTS: Sixty percent of the total patient group had baseline symptoms of agitation/aggression, delusions, or hallucinations on the NPI. At both 12 and 24/28 weeks, there was a significant treatment advantage for memantine over placebo for the proportion of patients showing improvement on the defined neuropsychiatric symptom cluster (55.6% vs. 44.4% at week 12, $p = .008$; 58.0% vs. 44.8% at week 24/28, $p = .002$) and specifically for the treatment of agitation/aggression (55.3% vs. 43.1% at week 12, $p = .011$; 61.0% vs. 45.0% at week 24/28, $p < .001$). Placebo-treated patients in this population demonstrated an accelerated disease progression for global (Clinician's Interview-Based Impression of Change Plus Caregiver Input), cognitive (Severe Impairment Battery), and functional (Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale) outcomes, but memantine conferred statistically significant benefit for all measures. Tolerability in this population remained good, and fewer memantine-treated patients than placebo-treated patients withdrew due to adverse events. CONCLUSIONS: This post hoc analysis provides important evidence from placebo-controlled trials that memantine may be a safe and effective treatment in Alzheimer's disease patients with agitation/aggression or psychosis, who are otherwise prone to rapid progression. Memantine treatment provided benefits in cognitive, functional, and global outcomes in these patients and for their agitation/aggression.

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