Antipsychotic drugs for psychosis and agitation in dementia: efficacy, safety, and a possible noradrenergic mechanism of action

The first patient described by Alzheimer in 1907 had both progressive cognitive deterioration and prominent comorbid signs and symptoms of psychosis and agitation (Alzheimer, 1907, 1987). In this editorial, we use “psychosis” to denote delusions and hallucinations and “agitation” to denote irritability, aggression, pressured motor activity, and active resistance to necessary care. Although advances have been made in the treatment of these non-cognitive symptoms, these psychosis and agitation symptoms continued to be burdensome and costly for dementia patients, caregivers, and society. Among the pharmacologic treatments available for psychosis and agitation, antipsychotic drugs are the drug class most consistently demonstrated effective for psychosis and agitation in dementia (Lyketsos et al., 2006; APA Work Group on Alzheimer’s Disease and Other Dementias et al., 2007). These are widely prescribed for these behavioral problems, but their use remains controversial and their mechanism of action unclear.

In this editorial, we attempt to discern from the clinical trial data which non-cognitive symptoms of dementia, if any, are therapeutically responsive to antipsychotics. We argue that despite the descriptor “antipsychotics,” (derived from their clear and substantial efficacy for the complex bizarre delusions and auditory hallucinations of psychosis in schizophrenia), the predominant effect of these drugs in dementia is to reduce agitation rather than psychosis. The most common psychosis symptoms in dementia are simple, memory impairment-influenced delusions (e.g., delusions of theft) and visual hallucinations. In contrast to agitation, these common psychosis symptoms in dementia are poorly responsive to antipsychotic drugs (Rabinowicz et al., 2007). We propose a model in which the therapeutic effect of antipsychotic drugs for agitation in dementia is a function of their alpha-1 adrenoreceptor (AR) antagonist activity rather than the dopamine receptor-2 antagonist activity, believed to explain efficacy for the psychosis symptoms of schizophrenia.

Although a detailed review of the now large number of randomized controlled trials (RCTs) of antipsychotic drugs for psychosis and agitation in dementia is beyond the scope of this editorial, we will refer to representative studies. In the 1980s and early 1990s, several “conventional” antipsychotics were evaluated for “behavioral disturbance” in dementia patients. Loxapine, thioridazine, and thiothixene were modestly effective, but pseudoparkinsonism and excessive sedation often limited usefulness (Barnes et al., 1982; Petrie et al., 1982; Finkel et al., 1995). The subsequently introduced atypical antipsychotics with lower incidences of extrapyramidal adverse effects became widely prescribed for behavioral disturbance in dementia, particularly in long-term care facilities (Kamble et al., 2009). Because these drugs were still under patent protection, several pharmaceutical companies saw an opportunity to obtain Food and Drug Administration (FDA) approval for risperidone, olanzapine, quetiapine, and aripiprazole as effective treatments for “psychosis of dementia” (Katz et al., 1999; Street et al., 2000; De Deyn et al., 2004; 2005; Mintzer et al., 2006; Tariot et al., 2006; Katz et al., 2007; Mintzer et al., 2007; Zhong et al., 2007; Streim et al., 2008). For both regulatory and diagnostic reasons, psychosis of dementia was designated as the primary outcome measure in these large multicenter RCTs. Drug effects on agitation were also measured, but as secondary outcome measures. Disappointingly, these RCTs generally failed to demonstrate meaningful efficacy for psychosis of dementia, the primary outcome measure upon which the FDA approval depended. In contrast, these RCTs consistently demonstrated efficacy for agitation symptoms in dementia. However, the secondary outcome measure designation of “agitation” and the nonspecifity of agitation as a disorder entity worked against the FDA approval of atypical antipsychotics for agitation in dementia. Further support for efficacy of the atypical antipsychotic risperidone for psychosis and/or agitation in Alzheimer’s disease (AD) is provided by a placebo-controlled study of relapse rate after discontinuing risperidone in treatment responders (Devanand et al., 2012). Discontinuation of
risperidone was associated with an increased risk of relapse.

A major safety issue that arose from the pharmaceutical industry development of antipsychotics for psychosis of dementia was a modestly increased risk of death in the active antipsychotic drug groups compared with the placebo groups. A paired analysis of 17 short-term RCTs revealed 1.6 times higher mortality among participants receiving antipsychotics than among participants receiving placebos (Schneider et al., 2005). This finding resulted in an FDA black box warning for these medications in dementia patients. The etiology of the increased mortality risk in these short-term studies remains unclear. Longer studies in community samples have failed to detect increased mortality risk in dementia patients treated with antipsychotics (Raivio et al., 2007; Simoni-Wastila et al., 2009). It is also possible that psychosis and agitation per se increase mortality and long-term institutionalization risks in dementia patients. A recent long-term longitudinal study of 957 patients with AD found that use of conventional and atypical antipsychotics was not associated with time to nursing home admission or death (Lopez et al., 2013). Rather, the presence of psychiatric symptoms, including psychosis and agitation, increased risk for institutionalization and death after adjusting for exposure to antipsychotics.

Because the published RCTs of antipsychotic drugs for behavioral disturbance in dementia generally do not present results for discrete psychosis and agitation signs and symptoms, it is difficult to dissect drug effects on specific types of psychotic behaviors (e.g., visual vs. auditory hallucinations) or components of agitation. Fortunately, Rabinowitz and colleagues (2007) evaluated the effects of the widely prescribed atypical antipsychotic risperidone on specific behavioral signs and symptoms in nursing home residents with AD or mixed etiology dementia. They performed a post hoc exploratory analysis of 479 patients who had participated in one of the three 12-week RCTs and who met criteria for psychosis in AD. Notably, patients in these trials who had agitation but not psychosis (the majority of participants) were not included in the analysis. In spite of selecting patients with moderate or severe psychosis symptoms, significant risperidone effects on individual items were limited to agitation symptoms and signs, including verbal and physical aggression pacing and irritability. Delusions of theft and hallucinations (visual twice as common as auditory) were particularly unresponsive to risperidone. A modestly significant (p = 0.03) therapeutic effect of risperidone was detected only when all psychosis symptoms were merged.

Other than the antipsychotics, the only drug effective for agitation in dementia in more than one placebo-controlled trials is the selective serotonin reuptake inhibitor (SSRI) citalopram. Nyth and Gottfries (1990) demonstrated efficacy of citalopram for agitation (and depression) symptoms in patients with AD but not in those with vascular dementia. In a short-term trial comparing citalopram with the antipsychotic perphenazine and placebo in dementia patients hospitalized for psychosis and/or agitation, citalopram was more effective than placebo (and tended to be more effective than perphenazine) for agitation but not for psychosis (Pollock et al., 2002).

A recently published multi-center placebo-controlled trial of citalopram in 186 AD patients with agitation provides evidence for clinically meaningful efficacy in this population (Porsteinsson et al., 2014). At a citalopram target dose of 30 mg per day, active drug was significantly superior to placebo for the Neurobehavioral Rating Scale – Agitation subscale, the Clinical Global Impression of Change, and caregiver distress scores. That citalopram was not significantly superior to placebo on the Neuropsychiatric Inventory – Agitation subscale (which is heavily loaded with aggressive behaviors) raises the possibility that overtly aggressive behaviors may be less responsive to citalopram than are other agitation behaviors. That said, citalopram is now clearly a treatment option for agitation in AD.

If agitation is responsive to citalopram and is the dementia behavioral disturbance most responsive to antipsychotics, then how can this be explained pharmacologically? We hypothesize that excessive brain noradrenergic system responsiveness contributes to the pathophysiology of agitation in AD. The well-known alpha-1 AR antagonist activity of antipsychotics (Roth et al., 2004; Nasrallah, 2008) and the less well-known but clearly demonstrated ability of SSRIs to decrease both locus coeruleus (LC) neuron norepinephrine (NE) biosynthetic capacity (Nestler et al., 1990) and LC neuron activity (West et al., 2009) could explain the ability of these drugs to reduce agitation in dementia. This hypothesis is consistent with the function of the brain noradrenergic system. Novel environmental stimuli and stressful events stimulate LC NE release to limbic and neocortical regions, increasing arousal and alertness and excessive brain noradrenergic activity, contributing to agitation behaviors, such as motor hyperactivity, irritability, and aggression (Berridge and Waterhouse, 2003; Ramos and Arnsten, 2007).

But how can this hypothesis be reconciled with the substantial loss of LC noradrenergic neurons that occurs in AD? Results of postmortem brain
tissue and clinical studies from our laboratory help resolve this paradox (Peskind et al., 1995; Elrod et al., 1997; Szot et al., 2006; 2007; Wang et al., 2009).

In spite of LC neuronal loss in AD (Tomlinson et al., 1981; Bondareff et al., 1982; Chan-Palay and Asan, 1989), measurements of NE and its metabolite 3-Methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (CSF) reveal equivalent levels to those of normal older persons and higher levels than those of normal young persons (Raskind et al., 1984; Elrod et al., 1997). When LC NE outflow is stimulated by yohimbine, AD patients demonstrate robust CSF NE increases that are equivalent to those of normal older patients and substantially greater than in young patients (Peskind et al., 1995); AD patients, but not normal older or young patients, developed agitation symptoms following yohimbine. Studies in postmortem brain tissue demonstrate compensatory changes in brain noradrenergic systems consistent with these clinical research findings. In AD (and in dementia with Lewy bodies), surviving LC neurons demonstrate increased NE biosynthetic capacity (Szot et al., 2006) and there is upregulation of postsynaptic alpha-1 AR and beta AR in limbic and neocortical LC neuronal projection areas (Russo-Neustadt et al., 1998; Szot et al., 2007).

Based on these findings, we evaluated clinically available CNS active AR antagonist drugs as potential therapeutic agents for agitation in AD. The beta AR antagonist propranolol was minimally and only transiently effective (Peskind et al., 2005) (note: antipsychotics do not have beta AR antagonist activity). Thus, beta AR upregulation does not appear to contribute substantially to agitation in AD. The alpha-1 AR antagonist activity common to all antipsychotic drugs and our demonstration of prazosin efficacy for agitation behaviors in post-traumatic stress disorder (Raskind et al., 2007; 2013) led us to evaluate prazosin for agitation in AD. Prazosin produced a robust and sustained decrease in agitation and improvement in global clinical status in AD patients with moderate to severe agitation (Wang et al., 2009). Notwithstanding its antihypertensive indication, prazosin gradually titrated upward and was well tolerated without hypotension at 2 mg in the morning and 4 mg in the evening. These results are consistent with the hypothesis that the alpha-1 AR antagonist activity of antipsychotics contributes to their ability to reduce agitation in AD. Because prazosin does not produce pseudoparkinsonism or sedation, this inexpensive drug may prove a useful therapeutic alternative to antipsychotics for agitation symptoms in AD and other later life dementias. A large multicenter RCT of prazosin for agitation in AD under the auspices of the National Institute on Aging-funded Alzheimer’s Disease Cooperative Study is scheduled to begin in late 2014.

Conflict of interest
None

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