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# Antipsychotics Versus Cholinesterase Inhibitors for the Treatment of Psychosis in Alzheimer's: A Critical Review

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## 1. Introduction

In the later stages of dementia, more than 50% of patients will experience behavioral and psychological symptoms of dementia (BPSD) including psychosis (Hemels, 2001). These symptoms reputedly cause distress in both patients and care-giving family members. Caregivers typically have reduced quality of life and see increases in the cost of care (Finkel, 1997; Herrmann, 2001), whereas patients tend to increase resource utilization and form a high-risk group for institutionalization (Daniel, 2000). Behavioral disorders being paramount, it is surprising that there is little agreement on the actual description of these symptoms (Stoppe, 1999). This reason among others, contributes to the perception that *"treating secondary symptoms of AD is more of an art than a science"* (Corey-Bloom, 1995).

In seeking pharmacological treatment options for psychotic symptoms in Alzheimer's disease, this review will attempt to address the following four questions: 1) What is the definition and clinical presentation of BPSD? 2) What is the prevalence and impact of psychotic symptoms on the progression of dementia in AD? 3) What are the indications for the use of antipsychotics in the treatment of BPSD? 4) What are the evidence-based treatments for BPSD?

## 2. Definition and clinical presentation of behavioral and psychological symptoms of dementia (BPSD)

In 1996, the International Psychogeriatric Association consensus group defined behavioral and psychological symptoms of dementia (BPSD) as: *"symptoms of disturbances of perception, thought content, mood or behavior frequently observed in demented patients"*.

Many classifications of BPSD have been proposed. When pharmacological treatment is concerned, classifying BPSD by syndromes is most useful. Although it is often difficult to

subgroup behavioral symptoms, psychological symptoms can be grouped into three syndromes: psychotic, depressive and delirious. A more descriptive classification summarizes the characteristic symptoms of BPSD in table 1.

Different BPSD appear at different stages of the illness. Affective symptoms tend to appear in the early stages of dementia (Reisberg et al., 1989; Rubin et al., 1988), whereas psychotic symptoms and agitation are more frequent in patients with moderate cognitive dysfunction. In fact, most BPSD are present prior to the later stages of the illness, when they abate possibly because of the physical and neurological deterioration of the patient (Tariot & Blazina, 1994).

### **3. Prevalence and impact of psychotic symptoms in dementia**

In a review of 30 studies of patients with AD, affective and psychotic symptoms were found to occur in 30%-40% of patients (Wragg & Jeste, 1989). However, up to 90% of patients living in institutions may suffer BPSD (Finkel, 1998). In patients with AD, the prevalence of psychotic symptoms alone is quite variable and was found to cluster around 20%-40% (Raskind & Barnes, 2002). In a study following patients longitudinally from the beginning to the later stages of AD, presence of psychotic symptoms was documented in over 50% of patients, and was more common at moderate and severe stages of dementia (42 to 84%) (Drevets & Rubin, 1989). Furthermore, in a one year longitudinal study, recurrence rates of psychotic symptoms in untreated patients have been estimated at 95% (Levy et al., 1996).

The two most common psychotic symptoms that develop in AD are delusions and hallucinations. The median prevalence of delusions is 36%, ranging between 9% and 63% (Ropacki and Jeste, 2005). Among the most frequent types of delusions identified are persecutory (involving theft) in 18-43% of patients followed by delusions of abandonment in 3-18% and delusions of jealousy (involving infidelity) in 1-9% (Tariot & Blazina, 1994). Hallucinations were estimated to vary between 4-41% hallucinations with a median of 18% (Ropacki and Jeste, 2005). Visual hallucinations were reported in up to 30% of moderately demented patients, whereas auditory hallucinations may occur in up to 10% of patients (Swearer, 1994). Other types of hallucinations such as olfactory, tactile, gustatory and haptic are rarely observed (Tariot & Blazina, 1994).

Aggression, one of the major behavioral symptoms in dementia, causes great distress in caregivers and can lead to earlier institutionalization (Chenoweth & Spencer, 1986; Rabins PV et al., 1982; Rabins et al., 1982). Delusions, mainly persecutory, have been identified as a risk factor for physical and verbal aggression in patients with AD (Deutsch et al., 1991). For instance, Deutsch et al. (1991) reported that out 181 AD patients, 43.5% suffered delusions, of which 29.6% were noted to be physically aggressive. Furthermore, delusions preceded and were significantly associated with aggressive behavior (Deutsch et al., 1991). The converse has also been shown in another study where 80% of patients with high levels of aggression (more than one episode/month) also presented with delusions (Gilley et al., 1997). This suggests that the presence of delusions predicts the frequency of physically aggressive behavior.

Increased rates of cognitive deterioration are also associated with psychotic symptoms in AD particularly in patients manifesting psychosis earlier in the course of dementia (Jeste et

al., 1992; Lopez et al., 1991; Stern et al., 1987). Interestingly, patients manifesting earlier psychotic symptoms were found to live longer than those without psychosis (Drevets & Rubin, 1989).

#### 4. Use of antipsychotics in the elderly

Though outside of the official FDA indication, in the elderly, atypical antipsychotics are most frequently prescribed for the treatment of behavioral symptoms of dementia. In May 2004, the FDA issued a warning of an increased death risk in elderly patients using atypical antipsychotics (Jeste et al., 2008). This warning was based on a meta-analysis of seventeen randomized double-blind controlled trials revealing a drug-related death risk increasing by 1.6-1.7 times when compared to placebo (Jeste et al., 2008). Most frequent causes of death were cardiovascular (heart failure or sudden death) and infectious (pneumonia). In April 2005, the FDA followed suit with a black box warning cautioning against the use of atypical antipsychotics in the elderly. Later the same year, a meta-analysis of 15 randomized controlled trials (Schneider *et al.*, 2005) examined the mortality risk between placebo and atypical antipsychotics as well as a comparison between various atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone). This study found a small increased mortality risk compared to placebo (OR = 1.54; 95%CI: 1.06-2.23). No difference was found between antipsychotics.

Given that this meta-analysis and the FDA warning did not apply to typical antipsychotics, the remaining assumption was that typical agents could be warranted in the treatment of BPSD. However, a study published in the New England Journal of Medicine compared the use of typical and atypical antipsychotics in the elderly and found that typical antipsychotics were associated with a significantly higher risk of death than atypical antipsychotics (Wang *et al.*, 2005). Hence, typical antipsychotics should not be used to replace atypical agents in the treatment of BPSD.

Currently, the FDA has not approved of any treatment for BPSD. Facing agitation in the elderly and consequent caregiver distress, clinicians are left with unclear choices. In the treatment of BPSD, what are the evidence-based alternatives?

#### 5. Evidence-based treatment-options for BPSD

##### Non-pharmacological options

In the treatment of BPSD, an initial assessment of the underlying causes of behavioral changes is necessary. Co-morbid medical illnesses and sensory impairment should be corrected prior to medication use. It has even been suggested that non-pharmacological approaches, including music therapy, light therapy, changes in stimulation, and specific behavioral techniques such as positive reinforcement could be attempted before medication (Beck & Shue, 1994; Opie et al., 1999). Although pharmacological treatment of BPSD should not be first line, high rates of psychotropic drug use have been reported, particularly in very old patients living in institutions (Giron, 2001). Between 39% and 51% of elderly institutionalized patients were found to be treated with antipsychotics (Avorn et al., 1989; Lantz et al., 1990). In the pharmacological treatment of BPSD, antipsychotic are the agents

that have been most frequently studied (Stoppe, 1999). In mild or moderate BPSD cases, particularly when symptoms are not interfering strongly with functioning, clinicians may opt not to treat BPSD. In such mild to moderate cases, psychosocial interventions (eg music therapy, cognitive therapy, behavioral management techniques, caregiver education) may have modest effectiveness (Cohen-Mansfield, 2001; Livingston et al, 2005).

In severe cases where psychotic symptoms and agitation interfere with functioning and cause significant caregiver distress, lack of treatment may be dangerous. Below we review the pharmacological treatment options for BPSD.

### Antipsychotics

A number of well-controlled trials predating the 2005 FDA warnings had examined the effectiveness of atypical antipsychotics in the treatment of BPSD. These studies are summarized and presented in Table 2. In the treatment of BPSD, atypical antipsychotics seem to be of significant though modest effectiveness. However, given the FDA black box warnings, much caution is necessary in using antipsychotics in the elderly.

The large NIMH funded Clinical Antipsychotic Trial of Intervention Effectiveness study for Alzheimer's Disease (CATIE-AD) trial found that olanzapine, quetiapine, and risperidone were no better than placebo in the treatment of psychotic symptoms of dementia. However, in a review of 15 randomized controlled trials (RCTs) of atypical antipsychotics for the treatment of BPSD, only risperidone was found to significantly improve psychosis scores (Schneider et al (2006).

### Cholinesterase inhibitors

There is some evidence supporting the relationship between cholinergic neurotransmission and behavioral symptoms of AD (Cummings & Kaufer, 1996). Given that neuropsychiatric changes in AD are associated with cholinergic deficits, one expects neuropsychiatric changes to respond to cholinergic therapy. Supporting this cholinergic hypothesis, Cummings (2000b) linked cholinergic deficits to behavior by identifying the following four dimensions of behavioral symptoms: *"1) induction of AD-like behaviours in normal individuals by administration of anticholinergic drugs; 2) the exaggeration of behavioural disturbances in AD patients by anticholinergic agents; 3) the correlation of the distribution of cholinergic deficits of AD with regions that are relevant to the observed behaviours, i.e. frontal and temporal regions; and 4) improvement of behavioural disturbances in AD patients treated with cholinergic receptor agonists and cholinesterase inhibitors"* (Cummings, 2000b).

Cummings also provides some compelling evidence that cholinesterase inhibitors have positive psychotropic effects in AD (Cummings, 2000a). For instance, patients with anticholinergic delirium (agitation and psychosis) were found to be similar to AD patients with non-cognitive symptoms (hallucinations and agitation). Given that these symptoms responded well to treatment enhancing cholinergic activity (Cummings, 1993), adjusting acetylcholine levels can reduce psychosis.

Displayed in table 3 are open label and double-blind studies on cholinesterase inhibitors (tacrine, donepezil, metrifonate, galantamine and rivastigmine) that have found reductions of non-cognitive behaviors over placebo.



A systematic review and meta-analysis quantified the efficacy of cholinesterase inhibitors as a group for neuropsychiatric symptoms in patients with mild to moderate AD (Trinh et al., 2003). This study found a modest beneficial impact on neuropsychiatric and functional outcomes. Other studies looking at the effects of galantamine (Hermann et al., 2005), donepezil (Holmes et al., 2004) and metrifonate (Kaufer, 1998) showed a modestly better outcome in behavioral symptoms than placebo-treated subjects. Another study compared memantine and placebo in AD patients treated with donepezil (Cummings et al., 2006 *Neurology*). Patients treated with donepezil and memantine had better behavioral outcomes than those treated with donepezil and placebo. Finally, a recent pooled analysis from six RCTs found a small but significant benefit from memantine in behavioral outcome scores (Gauthier et al., 2008).

Finally, one pilot open-label study assessed the safety of co-administration of rivastigmine with risperidone in dementia patients with behavioral disturbances (Weiser et al., 2002). The authors' main findings were two-fold: first, both these agents could be co-administered with no significant adverse effects and second, significant improvement in NPI scores were found in the rivastigmine-risperidone group of patients. These findings suggest that combination of these two agents might be more efficacious than either one alone (Weiser et al., 2002).

## 6. Conclusion

Addressing behavioral and psychological symptoms of dementia is paramount. Psychotic symptoms in AD occur in a majority of patients, and have a very high recurrence rate. Untreated BPSD can result in increased rates of hospitalization, institutionalization, cost of care and diminished quality of life for both patients and caregivers. Pharmacological treatment of BPSD should not be first line. Initial assessments of the underlying causes of BPSD are warranted and co-morbid medical illnesses should be corrected before initiating pharmacological treatment. In mild to moderate cases, non-pharmacological approaches (including music therapy, light therapy, changes in stimulation, and behavioral techniques) could be attempted before medications are used (Beck & Shue, 1994; Opie et al., 1999).

Given the FDA warnings, atypical antipsychotics should only be considered in moderate to severe cases on a case-by-case basis after careful evaluation of the risk-benefit ratio. The preferred antipsychotic seems to be risperidone as it was the only agent found in a meta-analysis of six RCTs to non-significantly increase mortality (Haupt et al., 2006) while another meta-analysis of fifteen trials found it to significantly improve psychosis scores (Schneider et al., 2006).

Facing the paucity of safe and effective medications available, cholinesterase inhibitors may be used as first line pharmacotherapy. Cholinesterase inhibitors have positive psychotropic effects in AD and are modestly effective in the treatment of BPSD. However, many AD patients are taking cholinesterase inhibitors and nevertheless develop BPSD. In such cases, the augmentation with memantine (Cummings et al., 2006) or risperidone (Weiser et al., 2002) may be warranted. More studies examining the combination of cholinesterase inhibitors with other agents are warranted.

- Behavioral Symptoms

Aggression

Wandering

Agitation

Yelling

Disinhibition

Pacing
- Psychological Symptoms

Delusions

Hallucinations

Depressed mood

Insomnia

Anxiety

Misidentification

Table 1. Slassification of behavioral and psychological symptoms of dementia (BPSD).

Reference	Study Type/ Duration	n	Rx types	Dose (mg/d)	Neuro scales	Outcome
(Frenchman & Prince, 1997)	Retrospective chart review	186	Risperidone (n=60)	-Mean risperidone= 1 mg/d		Target behaviors (including paranoia and delusions) improved in more patients on risperidone (94%) than haloperidol (65%), and thioridazine (67%) (p < .001).
			Haloperidol (n=83)	-Mean haloperidol= 2 mg/d		
			Thioridazine (n=43)	-Mean thioridazine= 33 mg/d		
(Goldberg & Goldberg, 1997)	Open / 6 months	109	Risperidone	0.5-1 (range)		Delusions improved in 75% of patients and Hallucinations in 73%.
(Irizarry et al., 1999)	Retrospective / 16 months	41	Risperidone	1.8 1.4 (mean sd)	4-point-scale constructed by authors	Psychosis improved partially in 41% with AD, completely in 15%.
(Katz et al., 1999)	Double-blind / 12 wk	625	Risperidone	0.5-2 (range)	BEHAVE-AD	Improvement in total scores and psychosis sub-scale scores of BEHAVE-AD for 1-2mg/d.
(De Deyn et al., 1999)	Double-blind / 12 wk	344	Risperidone Haloperidol	0.5-4 1.1	BEHAVE-AD	Significant difference from baseline in total scores of BEHAVE-AD in risperidone group only.
(Jeste et al., 2000)	Open / 12 month	330	Risperidone	0.5-2 (range)	BEHAVE-AD	Improvement on total and psychosis sub-scale scores of BEHAVE-AD for 0.75-1.5mg/d (p=0.03).
(Street et al., 2000)	Double-blind / 6 wk	206	Olanzapine	Fixed doses of 5-10-15 mg/d or placebo	NPI-NH	Significant improvement at 5mg/d (p<0.001) and 10 mg/d (p=0.006) on core symptoms including hallucinations & delusions.

Table 2. Part I.

(Clark et al., 2001)	Double-blind / 6 wk	206	Olanzapine	Fixed doses of 5-10- 15mg/ d vs. placebo	NPI-NH	-Significantly greater emergence of delusions and hallucinations for placebo vs olanzapine (p=0.006) in patients without at baseline. -Significantly greater emergence of hallucinations for placebo vs olanzapine (p=0.026) in patients without at baseline.
(Street et al., 2001)	Open / 18 wk	105	Olanzapine	5-15	NPI-NH	Significant improvement in 'Core total items' on NPI-NH (p=0.002) and NPI-NH total scores (p<0.001).
(Satterlee et al., 1995)	Double-blind / 8 wk	238	Olanzapine	1-8	BEHAVE-AD	No statistical significant differences between placebo and olanzapine.
(McManus et al., 1999)	Open / 52 wk	151	Quetiapine	25-800	BPRS (18- item) & CGI-severity of illness	Significant improvement at 12 wks on both BPRS (p<0.0001) and CGI (p<0.01).
(Scharre & Chang, 2002)	Open / 12 wk	10	Quetiapine	50-150	NPI	Significant improvement on total NPI score (p=0.002) and delusion sub-scale score (p=0.02) at wk 12.
(Chengappa et al., 1995)	Retrospective chart review / 30 month	12	Clozapine	25-300	survey	2/12 showed significant and 5/12 moderate improvement in psychosis.
(Oberholzer et al., 1992)	Open / 0.2-22 months	18	Clozapine	12.5-200	NOSIE <sup>1</sup> & SCAG <sup>2</sup>	Improvement in NOSIE score for psychotic symptoms but not significant (p=0.76).
(Salzman et al., 1995)	Retrospective chart review / 2-14 months	20	Clozapine	Average dose=208	NA	Modest reduction in psychotic symptoms.

Part II

1 - NOSIE = Nurses' Observation Scale for Inpatient Evaluation  
2 - SCAG = Sandoz Clinical Assessment Geriatric Scale  
NPI = Neuropsychiatric Inventory, NPI-NH: Neuropsychiatric Inventory Nursing Home Version  
BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease Rating Scale  
BPRS = Brief Psychiatric Rating Scale  
CGI-S = Clinical Global Impression-Severity of Illness Scale  
NA = Not Available

Table 2. Treatment of psychosis in AD: Atypical antipsychotics.



Reference	Study Type / Duration	n	Rx types	Dose (mg/d)	Neuro scales	Outcome
(Kaufer et al., 1996)	Open / 24 wks	28	Tacrine	40-160	NPI	-Mean NPI score was markedly decreased at 120mg/d (p=0.04) and 160mg/d (p=0.01) of tacrine. -Symptoms including hallucinations were most improved.
(Raskind et al., 1997)	Retrospective analysis of Randomized-Placebo-controlled / 30wk	415	Tacrine	160	ADAS-non-cog	Significant improvement or stabilization on ADAS-non-cog scores for scale items including delusions (p<0.05).
(Qizilbash et al., 1998)	Meta-analysis of double-blind trials / 12 wk	2021	Tacrine	20-160	ADAS-non-cog	Small but significant difference in ADAS-non-cog favoring tacrine at 12 wks (p=0.006).
(Knapp et al., 1994)	Double-blind / 30wk	663	Tacrine	40-160	ADAS-non-cog	No significant difference between placebo and doses of 80, 120, 160 mg/d.
(Farlow et al., 1992)	Double-blind / 12wk	468	Tacrine	20-80	ADAS-non-cog	No statistical differences at week 6 & 12 for dose-related improvement.
(Davis et al., 1992)	Double-blind / 6 wk	215	Tacrine	40 or 80	ADAS-non-cog	No statistical differences in mean scores in both groups.
(Feldman et al., 2001)	Double-blind / 24wk	219	Donepezil	5-10	NPI	Significant difference in favor of donepezil at wks 4 (p=0.03) & 24 (p=0.008).
(Gauthier et al., 2002)	Double-blind / 24 wk	207	Donepezil	5-10	NPI	Significant differences with placebo at wk 4 & 24 (p=0.0022).
(Mega et al., 1999)	Open label retrospective study	86	Donepezil	5-10	NPI	-Improvement in 41% of patients; 28% worsened and 31% unchanged. -Responders had worse delusions at baseline (p=0.04). -Significant change from baseline for delusions in responders (p=0.004) and worsening in non-responders (p=0.003).
(Matthews et al., 2000)	Open / 18 months	80	Donepezil	5-10	NPI	37% of patients improved at 3 months; of those patients, improvements were sustained at 18 months.
(Tariot et al., 2001)	Double-blind / 24 wk	208	Donepezil	5-10	NPI-NH	No statistical difference in mean NPI total scores between placebo and donepezil.
(Winblad et al., 2001)	Double-blind / 52 wk	286	Donepezil	5-10	NPI-NH	No statistical differences in total NPI scores.

Table 3. Part I

(Morris et al., 1998)	Double-blind / 36 wk	408	Metrifonate	30-60	NPI & ADAS-non- cog	-Significant differences for mean total NPI scores (p=0.0161). -No statistical differences favoring metrifonate with ADAS-non-cog.
(Kaufer, 1998)	Double-blind / 26 wk	408	Metrifonate	30-60	NPI	Statistically significant mean change differences in total NPI scores (p=0.07) and in symptoms including hallucinations (p=0.0002).
(Cummings et al., 1998)	Double-blind / 26 wk	1218	Metrifonate	Low dose (LD): 50 fixed or 30-60 or High dose (HD): 60 or 80	NPI	-Both HD (p=0.0392) and LD (p=0.002) significantly improved total NPI scores. -Hallucinations were most responsive to metrifonate in a dose-related manner (p=0.028 for LD; p=0.012 for HD).
(Raskind et al., 1999)	Double-blind / 26 wk	264	Metrifonate	50	NPI & ADAS-non- cog	Improvement in total NPI scores (p=0.013) but not with ADAS-non-cog.
(Tariot et al., 2000)	Double-blind / 5 mo	978	Galantamine	8 or 16 or 24	NPI	16 & 24mg/d groups improved significantly on total NPI scores (p<0.05) but 8mg/d and placebo groups deteriorated on total NPI scores.
(Bullock et al., 2001)	Open / 26wk	113	Rivastigmine	3-12	NPI-NH	-53% of patients with behavioral symptoms showed improvement. -Up to 93% of patients without behavioral symptoms did not develop these symptoms.
(Etemad, 2001)	Open / 26 wk	181	Rivastigmine	12	NPI-NH	Significant behavioral improvement (decrease by 4 points on mean total NPI score).
(Cummings et al., 2000a)	Open / 26 wk	173	Rivastigmine	3-12	NPI-NH	-Significant behavioral improvement (decrease by 3.25 points on mean total NPI score). -Significant improvement in psychosis sub-scale scores.
(Rosler et al., 1998)	Placebo-controlled / 26 wk Open / 104 wk	34	Rivastigmine	6-12	CIBIC-Plus	Statistical difference in the groups (p=0.02).  Significant behavioral improvement at week 52 for hallucinations.

Part II

CIBIC-Plus: Clinician’s Interview-Based Impression of Change Plus scale  
ADAS-non-cog: Non-Cognitive portion of the Alzheimer’s Disease Assessment Scale

Table 3. Cholinesterase inhibitors for psychosis in AD.

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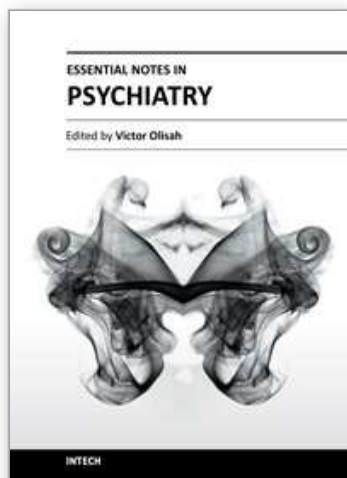


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