The place for treatments of associated neuropsychiatric and other symptoms

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Public Declaration of transparency/interests*

Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator	X				
Individual's Institution/Organisation receives a grant or other funding	X				
CME Courses				X	

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Note: For this presentation I am not receiving any compensation

Neuropsychiatric Symptoms (NPS) of dementia

Aggression, Agitation, Depression, Anxiety, Delusions, Hallucinations, Apathy, Disinhibition

Affect individuals with dementia nearly universally across dementia stages and etiologies.

EMA and FDA have never approved specific pharmacotherapy for NPS in Dementia, psychotropic medications are frequently used to manage these symptoms, but in the few cases of proven pharmacological efficacy, significant risk of adverse effects may offset benefits.

J Am Geriatr Soc. 2014 Apr;62(4):762-9.

NPS: core features of AD and other Dementias.

In one study, neuropsychiatric symptoms in patients with AD were highly prevalent (91% of patients), with 63% of patients having agitated and/or aggressive behaviours (Craig et al. 2005).

Agitation/aggression is clinically significant in approximately 20% of people with dementia in a community setting and in nearly 50% of people in care facilities (Lobo et al. 2000).

It has been consistently demonstrated that cognitive decline, behavioural disturbances, and depression associated with AD are strong predictors of nursing home admission, across numerous studies.

Risperidone

There is only one pharmacological treatment approved in Europe for the management of a specific subset of behavioural symptoms in AD.

Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe AD unresponsive to nonpharmacological approaches and when there is a risk of harm to self or others.

All Conventional and Atypical Antipsychotic medicinal products in Patients with AD, are used therefore as: **”off label”!**

Background

2004 – CSM advises MHRA of increase risk of stroke with the use of risperidone or olanzapine in the elderly with dementia. Warning issued.

2005 – Europe wide review concludes that this risk could not be excluded for other antipsychotic agents (either typical or atypical) – product information for all antipsychotics was updated to include class warning.

2005 – US FDA issued a warning that the treatment of behavioural disorder in dementia with atypicals is associated with an increased risk of death.

2005 – US and Europe – similar conclusions – product info updated to include increased risk of mortality (and a caution added to SPC of risperidone – increased risk of death when co-prescribed with furosemide).

CHMP assessment report on Conventional antipsychotics

The CHMP opinion was sought on the following:

1. The strength of the evidence to suggest that conventional antipsychotics are associated with excess mortality when used in elderly people with dementia;
2. The strength of the evidence to suggest that conventional antipsychotics are associated with a greater risk of mortality compared with atypical antipsychotics;
3. Whether or not the risk can/should be extrapolated to those conventional antipsychotics not included in the studies;
4. The need to conduct further studies, including on the possible mechanisms underlying the increase in mortality observed.

Background

2006 – NICE publishes Clinical Guideline 42. Dementia: Supporting people with dementia and their carers in health and social care – advising prescribers should avoid using any antipsychotics (second generation or conventional) for non-cognitive symptoms or challenging behaviour of dementia unless the patient is severely distressed or there is an immediate harm to them or others.

2008 – FDA issued an alert to healthcare professionals in US about the risk of using typicals in dementia. EMA reviews use of conventional antipsychotics in elderly patients with dementia.

2008 – Risperidone gains license to treat dementia related behavioural disturbances in Alzheimer‘s disease for up to six weeks.

2009 – Long term follow-up data from DART-AD suggest difference in mortality with all antipsychotics. MHRA concludes – clear increased risk of stroke and a small increased risk of death when any antipsychotic is used in elderly people with dementia

Impact of safety warnings on antipsychotic prescriptions in dementia: Nothing has changed

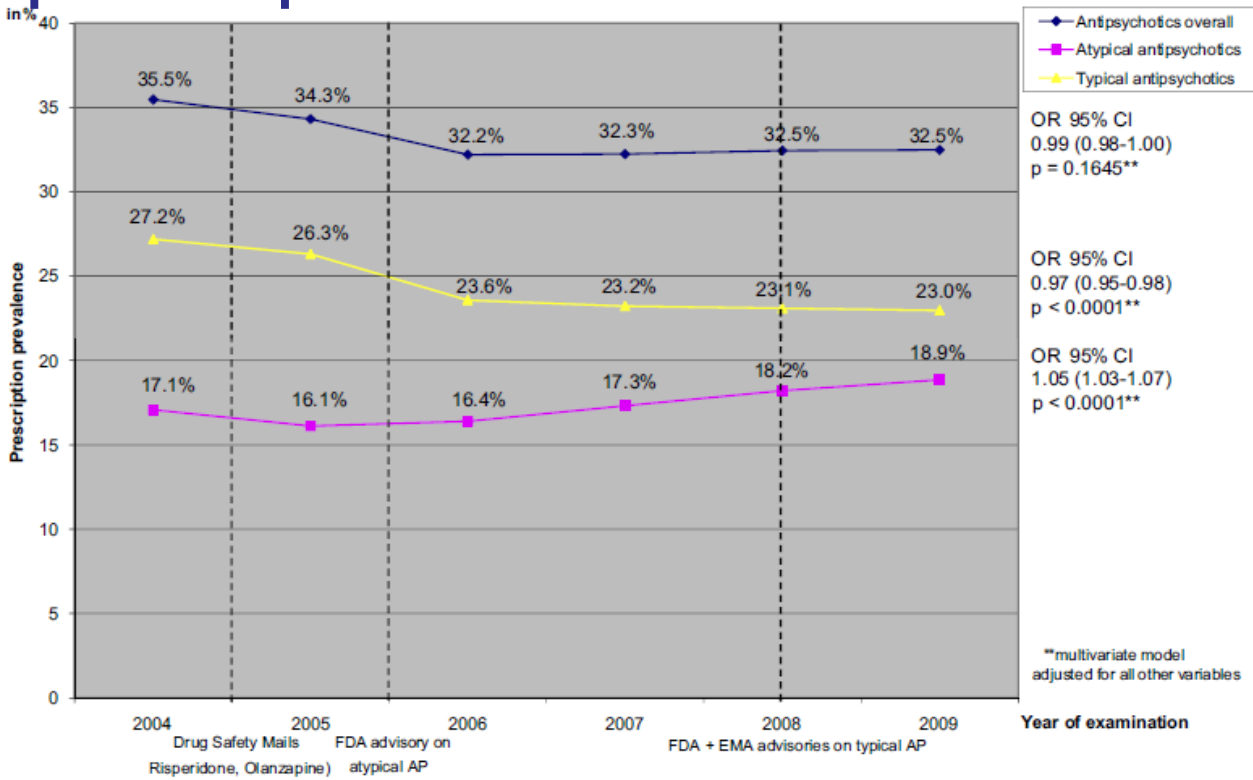

Figure 1 Prescription trends in antipsychotics from 2004 to 2009.

There is a shift in prescriptions from typical to atypical agents, while the overall prescription behavior of antipsychotics in dementia patients has not been changed significantly from 2004 to 2009.

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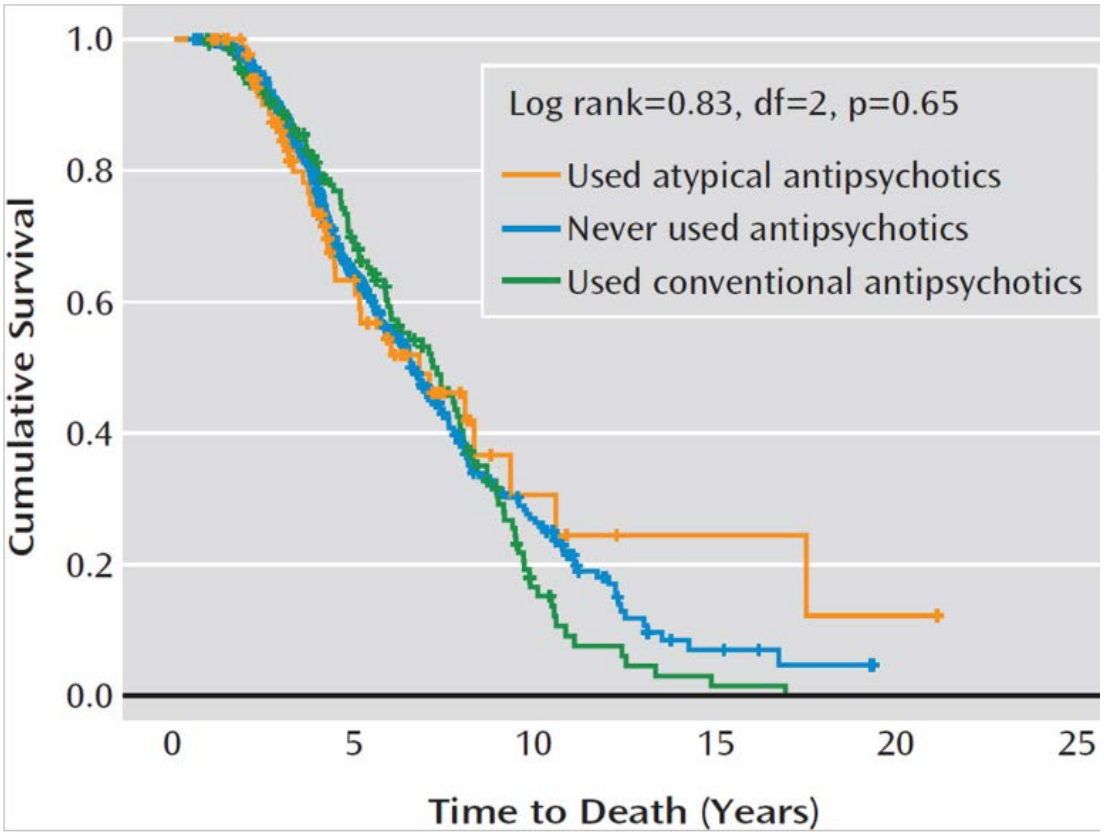
European Neuropsychopharmacology (2013) 23, 1034–1042

The Long-Term Effects of Conventional and Atypical Antipsychotics in Patients with AD



Kaplan-Meier Survival Analysis of Time to Death in Patients With Probable Alzheimer's Disease and Antipsychotic Use

An higher rates of psychosis, aggression, agitation, and antidepressant use and a lower rate of dementia medication use among those who used antipsychotics. Patients treated with conventional and atypical antipsychotics had more psychosis and aggression than those who had never taken antipsychotics.

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Am J Psychiatry. Sep 1, 2013; 170(9): 1051–1058

Safety of antipsychotics in behavioral disorders in elderly people with dementia: last 10 y update

A MEDLINE search

Atypical antipsychotics: efficacy > to placebo in randomized studies in BPSD treatment, with better tolerability vs. conventional drugs. However, factors to be seriously considered before prescribing an antipsychotic drug:

- The presence of cardiovascular diseases;
- QTc interval on electrocardiogram;
- Electrolytic imbalances;
- Familiar history for Torsades des pointes;
- Concomitant treatments, and use of drugs able to lengthen QTc.

J Clin Psychopharmacol. 2014 Feb;34(1):109-23.

The main goals in treating Dementias

- Primary prevention of symptomatic disease by intervention in suspected pathogenic mechanism at a pre-symptomatic stage
- Disease modification with slowing or arrest of symptom progression and evidence of delay in the underlying pathological process
- Symptomatic improvement, which may consist in enhanced cognition, functional improvement and/or improvement in neuropsychiatric and behavioural dysfunction
- Stand alone symptoms as part of AD may also be treated, *e.g.* agitation/aggression, depression and/or other neuropsychiatric symptoms

Management of behavioural problems in AD

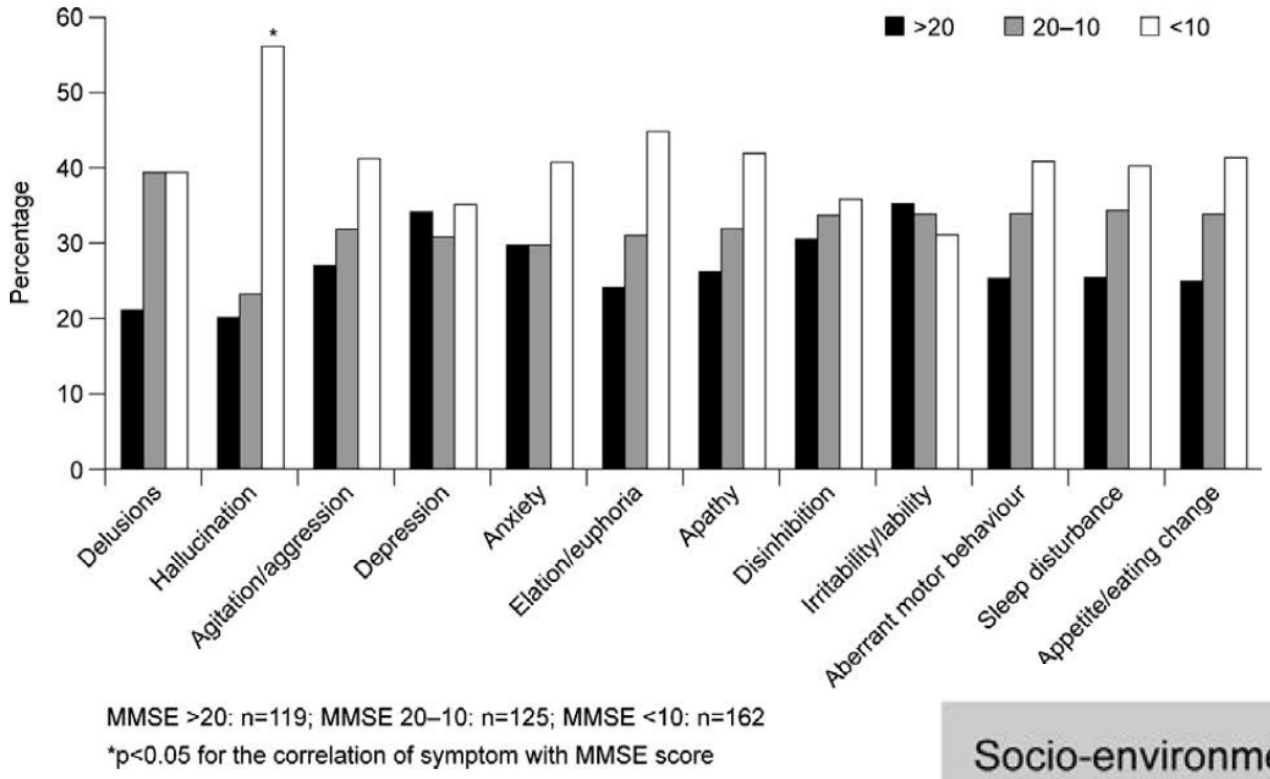
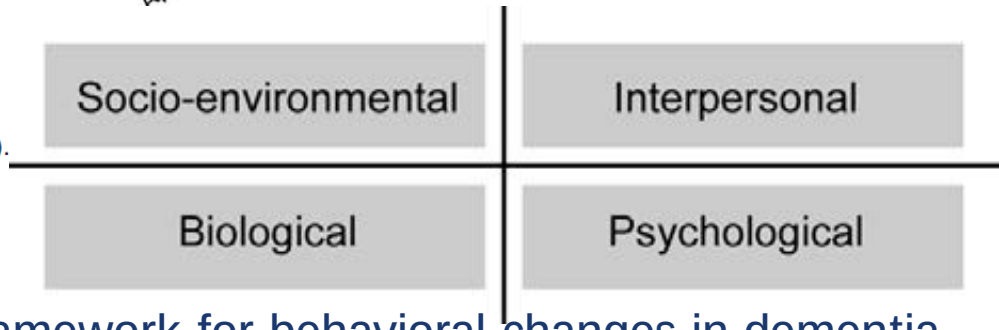


Figure 2. NPI symptoms in AD, by MMSE groupings (mild, moderate, severe) (Craig *et al.*, 2005).

NPS are grouped into three syndromes:

1. **Psychotic:** (agitation, hallucinations, delusions, irritability)
2. **Mood:** (anxiety, depression)
3. **Frontal:** (disinhibition, euphoria)

Frisoni et al. (1999)



The bio-psycho-social framework for behavioral changes in dementia.

International Psychogeriatrics (2010), 22:3, 346–372

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Which possible pathway?

In this scenario, the development of products for symptomatic treatment of NPS is encouraged, in parallel with the development, validation and use of reliable and sensitive instruments to measure cognition, functional, behavioural and neuropsychiatric symptoms especially in early disease stages.

CTs secondary endpoints in the context of symptomatic treatment of AD, should include neuropsychiatric and behavioural symptoms, measured using specific and validated scales, as part of the confirmatory testing strategy.

It is recommended to address these additional hypotheses through a separate trial.

NPS: as stand-alone indication

- In general symptomatic treatment of AD includes NPS.
- In order to be a stand-alone indication the mechanism of action of the AS should be relevant and specific for the treatment of NPS.
- Symptoms in early stages are different from the later stages of disease and issues of «pseudospecificity» should be considered.
- Furthermore, cognition and function should be measured in these trials as secondary end points in order to exclude a deteriorating effect on these domains.

Behavioural signs and symptoms

Although the formal clinical diagnostic criteria do not include behavioural signs and symptoms, they are:

- An important cause of clinical deterioration in patients with advanced stages of dementia
- Associated with increased burden of disease and stress for family members and caregivers.

The frequency and severity of behavioural abnormalities increase with the progression of AD.

Furthermore, individual behavioural symptoms have been described as highly variable and heterogeneous in presentation, transient, recurrent or persistent in course and fluctuating in prevalence and severity.

How to evaluate a symptomatic improvement?

An ideal approach

Neuropsychiatric and behavioural symptoms improvement, measured using specific and validated scales, can be highly variable and heterogeneous in presentation, transient, recurrent or persistent in course and fluctuating in prevalence and severity.

The medicinal product should be specific for the treatment of neuropsychiatric symptoms (*e.g.* agitation, apathy) requiring reliable and valid measurement tools for the studied patient population in the determined stage of the Diseases.

Study duration depends on the symptoms typology and should be justified.

With which assessment tools?

Possible assessment tools, to be used as outcomes measurement in CTs, are the following:

1. Behavioural pathology in Alzheimer's disease rating scale (BEHAVE-AD);
2. Behavioural Rating Scale for Dementia (BRSD);
3. Neuropsychiatric Inventory (NPI)

Newer tools are and should be under development to reflect different characteristic signs and symptoms in accordance with different disease stages.

Questions

Which level of flexibility could be acceptable in a CT's Design to assess multiple NPSs related to the different stadium of evolution of AD, considering its continuous progression?

Which criteria can be objectively used to define clusters of patients?

Is it necessary to consider as outcome the positive effect of the treatment on a cluster of symptoms or is better to evaluate the result on each single NP symptom but losing their mutual complex correlation?

Is it correctly recommended to address a separate Trial for NPSs outcome without taking into consideration the potential effect of the treatment on the cognitive disability progression?

Is a psychometric tool like a closed answers questionnaire enough to evaluate a behavioral change or could be necessary supplement the interview with other techniques like neuroimaging studies?