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Mcgill review course for Family medicine

Behavioral and Psychological Symptoms in Dementia:
A Review

M. Elie, M.D., FRCPC
Conflict of Interest

McGill Faculty of Medicine
66th Annual Refresher Course for Family Physicians

NONE
OBJECTIVES

1. Review Prevalence and Differential diagnosis of Behavioral and Psychological Symptoms of Dementia

2. Review its Management and Outcome
Another nail in the coffin of the cognitive paradigm of dementia

Alistair Burns

Summary
An emerging appreciation by practitioners and researchers, long held by patients and carers, is that neuropsychiatric features of dementia and the challenges they present are as important as those of cognitive losses.

Declaration of interest
A.B. has received research funding, honoraria and expenses for consultancy work from companies involved in the manufacturing and marketing of drugs for dementia: Baxter, Eisai, Janssen, Lundbeck, Novartis, Pfizer and Shire.

When Alois Alzheimer described his first patient in 1906 she had prominent psychiatric symptoms (delusions that Alzheimer meant her harm) and behavioural problems (screaming). It was the combination of these symptoms and organic brain changes (senile plaques and neurofibrillary tangles identified histologically) in a younger person (she was aged 51 when the disease started and died 4.5 years later) which set the case apart and earned the eponym Alzheimer’s disease. Despite these prominent features, the cognitive paradigm of Alzheimer’s disease was established with memory and language disorders being regarded as the primary symptoms with psychological and behavioural problems being at the very least secondary, if not merely epiphenomena. It was only in the 1980s and 1990s that the importance of the symptoms became apparent, prompted by recognition of their importance to carers, the development of treatments to control positive symptoms and to curb behaviours, and the ability to make valid measurements of their presence and impact.

Terminology

unsurprisingly, the two have much in common. Until fairly recently, people with dementia did not present until later in their illness and the emphasis on people with more advanced disease led to greater consideration of behavioural disturbances. Later, the full appreciation of the relevance of the range of psychiatric symptoms occurring earlier in the disease emerged, not only positive psychopathology (e.g. delusions and hallucinations), but negative symptoms (e.g. apathy) as well. Personality changes are almost universal and coarsening of affect is often described. What is important is that they have emphasised the key role that emotional changes play as experienced by both the person with dementia and as observed by others.

Although Alzheimer’s disease is the paradigm by which other dementias are compared, differences in phenomenology have been documented. Vascular dementia may be associated with increased depression, Lewy body dementia is partly defined by the presence of hallucinations and paranoid ideas, personality change is predominant in frontal lobe dementia, and lack of initiation is a hallmark of the subcortical dementia associated with vascular disease, progressive supranuclear palsy and Parkinson’s disease.

Linking psychopathology to biomarkers has been successful in showing correlational rather than causal associations. Associations between general ratings of neuropsychiatric features and brain changes underscore biological mechanisms and have been demonstrated with regional atrophy on computed tomography
Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population†

George M. Savva,* Julia Zaccai,* Fiona E. Matthews, Julie E. Davidson, Ian McKeith, Carol Brayne, of behalf of the Medical Research Council Cognitive Function and Ageing Study

Background
Behavioural and psychological symptoms of dementia (BPSD) are major contributors to the burden of dementia.

Aims
To describe the prevalence, correlates and course of BPSD in the population of England and Wales.

Method
The prevalence of 12 symptoms was estimated in 587 participants with dementia and 2050 participants without dementia as part of a population-based longitudinal study of ageing. The effect of risk factors and the factor structure were estimated using 1782 interviews provided by participants with dementia throughout the study.

Results
Each symptom apart from sleeping problems was more common in the population with dementia. The co-occurrence

Conclusions
Behavioural and psychological symptoms of dementia affect nearly all people with dementia. Symptoms co-occur, and the symptoms that affected individuals experience are related to their socio-demographic and clinical characteristics.

Declaration of interest
This study was funded by a grant from GlaxoSmithKline. The Cognitive Function and Ageing Study is supported by the Medical Research Council.
“Quantification and Qualification of the behavior is most important in its understanding and treatment”
<table>
<thead>
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<th>Behavioural Disturbances</th>
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<td>Hallucinations</td>
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<td>Restlessness</td>
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<td>Wandering</td>
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<td>Sundowning</td>
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</tbody>
</table>
DIFFERENTIAL DIAGNOSIS

“Behavior / Agitation”

Pain
Medical

Differential Diagnosis

Depression
Environmental

Management and Pharmacological
or Behavior

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Treatment
BEHAVIORAL...
Nonpharmacologic Interventions for Psychotic Symptoms in Dementia

Jiska Cohen-Mansfield, PhD, ABPP

ABSTRACT

This article proposes an initial nomenclature and systematic approach for the nonpharmacologic understanding and treatment of psychotic symptoms in dementia. An analysis of delusions and hallucinations must examine alternative etiologies, including misdiagnosis and misunderstanding, the misinterpretation of reality because of cognitive losses, sensory deprivation and vision loss, ambiguous sensations, and delirium and medical causes. Nonpharmacologic treatments frequently follow directly from etiology, such as improving sensory function via hearing aids or eyeglasses, providing stimulation, changing antecedents prone to misinterpretation (e.g., reflections in windows), or circumventing misinterpretations (e.g., ensuring that an equivalent object is available so there is no sense of loss or theft). Given the differences between psychotic symptoms in Alzheimer’s disease and those in other diseases, the term psychosis should be abandoned for most dementia patients, and assessments of etiology should be developed. Future research should clarify what proportion of symptoms currently identified as psychotic are attributable to related etiologies. (J Geriatr Psychiatry Neurol 2003; 16:219-224)

Keywords: behavioral interventions; psychosocial and environmental treatments; psychosis; delusions; hallucinations

There is very little information available about nonpharmacologic approaches to delusions and hallucinations, despite research and clinical findings that suggest the benefits of nondrug interventions. Within this framework, this article addresses the following issues: the definition and subtypes of psychotic symptoms, the etiology of psychotic symptoms, the nonpharmacologic treatment of psychotic symptoms, barriers to the use of nonpharmacologic approaches to the treatment of psychotic symptoms, and patients diagnosed with schizophrenia. They differ in overall incidence, the prevalence of specific subtypes and symptoms, history, the frequency of remission, treatment practices, and the qualitative nature of symptoms. Very few AD patients have histories of psychosis or bizarre delusions. To the contrary, it is common for elderly persons with schizophrenia to have suffered psychosis in their past, including bizarre or complex delusions. Furthermore, hallucinations tend to be visual in AD and auditory in schiz-
Often trial and error, need to inform and communicate with family / caregivers...
PHARMACOLOGICAL...cont’d

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Acetylcholinesterase Inhibitors
(± Memantine)
Efficacy of Cholinesterase Inhibitors in the Treatment of Neuropsychiatric Symptoms and Functional Impairment in Alzheimer Disease: A Meta-analysis

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Subhanjoy Mohanty, PhD
Kristine Yaffe, MD

ALZHEIMER DISEASE (AD) is the most common form of dementia, accounting for more than 50% of all dementia cases, and the number of affected individuals will likely quadruple over the next several decades. Research in the treatment of AD has focused on reducing cognitive decline with cholinesterase inhibitors (ChIs), the primary class of medications currently available for this purpose. However, neuropsychiatric symptoms and functional deficits also contribute greatly to the disability associated with AD. As many as 80% of patients with AD will experience neuropsychiatric symptoms such as hallucinations, paranoia, agitation, and

Context Cholinesterase inhibitors are the primary treatment for the cognitive symptoms of Alzheimer disease (AD). Cholinergic dysfunction is also associated with neuropsychiatric and functional deficits, but results from randomized controlled trials of cholinesterase inhibitors are conflicting.

Objective To conduct a systematic review and meta-analysis to quantify the efficacy of cholinesterase inhibitors for neuropsychiatric and functional outcomes in patients with mild to moderate AD.

Data Sources We performed a literature search of trials using MEDLINE (January 1966–December 2001), Dissertations Abstracts Online, PSYCHINFO, BIOSIS, PubMed, and the Cochrane Controlled Trials Register. We retrieved English- and non-English-language articles for review and collected references from bibliographies of reviews, original research articles, and other articles of interest. We searched for both published and unpublished trials, contacting researchers and pharmaceutical companies.

Study Selection We included 29 parallel-group or crossover randomized, double-blind, placebo-controlled trials of outpatients who were diagnosed as having mild to moderate probable AD and were treated for at least 1 month with a cholinesterase inhibitor. Sixteen trials included neuropsychiatric and 18 included functional measures.

Data Extraction Two investigators (N.H.T. and J.H.) independently extracted study methods, sources of bias, and outcomes. Neuropsychiatric outcomes were measured with the Neuropsychiatric Inventory (NPI, 0-120 points) and the Alzheimer Disease Assessment Scale, noncognitive (ADAS-noncog, 0-50 points) and were analyzed with the weighted mean difference method. Functional outcomes were measured with several activities of daily living (ADL) and instrumental activities of daily living (IADL) scales and analyzed with the standardized mean difference method.
Antipsychotics (Atypical and Typical)
Neuroleptic drugs in dementia: benefits and harm

Clive Ballard and Robert Howard

Abstract | Neuroleptic (antipsychotic) drugs are often used to treat psychiatric symptoms frequently seen in dementia, but their use is controversial. We present a new meta-analysis to assess the efficacy of these drugs for the treatment of psychiatric symptoms in Alzheimer's disease, and discuss the more limited evidence for their potential benefits in other dementias. We recommend that these treatments be limited to the short-term treatment of psychiatric symptoms associated with serious distress or risk.

Worldwide, 25 million people suffer from dementia, most of whom have Alzheimer's disease (AD). This is a devastating illness that results in a progressive decline in cognitive ability and functional capacity, causes immense distress to patients and their carers and families, and has an enormous societal impact. There are a myriad of research priorities and clinical treatment issues. These include the development and use of treatments that ameliorate disease progression; the development of diagnostic markers to allow treatment of people with very early AD; the improvement of therapies for AD; and an improvement in our knowledge of risk factors for AD, such that its incidence might be reduced. Although these are all vital long-term goals, the most frequent treatment issue for people with AD presenting to clinical services remains the management of behavioural symptoms. More than 90% of people with dementia develop neuropsychiatric symptoms at some stage during their illness. These symptoms to be effective. Many people self-medicate with over-the-counter herbal remedies and, until a recent trial indicated the potential for harm, hormone replacement therapy was prescribed by some specialists as a treatment for AD (its therapeutic use had been based largely on anecdotal evidence).

There is a clear need to treat the psychiatric and behavioural symptoms in people with dementia — besides the distress to patients themselves, there is the potential risk of physical injury to others as a consequence of aggression, the despair of caregivers, and the likelihood of the family situation 'breaking down'. However, the evidence for most pharmacological treatments other than neuroleptics (also known as antipsychotics) is limited, and during the past 18 months the US Food and Drug Administration (FDA) and the UK Committee for Safety of Medicines (CSM) have issued statements highlighting serious safety concerns about the use of neuroleptics in individuals with dementia.

In the face of this major clinical dilemma, who are in contact with clinical services or living in the community, frequencies are higher (40–60%) in care facilities. The most frequent psychotic symptoms, each of which are present in ~25% of people with dementia in clinical settings, are visual hallucinations, auditory hallucinations and persecutory delusions. First rank symptoms of schizophrenia almost never occur in individuals with dementia, and, in contrast to functional psychoses, the psychotic symptoms seen in dementia are much less complex, usually visual or second-person auditory hallucinations of people or animals, and simple persecutory delusions such as believing that possessions have been stolen. In a recent community study, ~18% of people with AD experienced delusions and ~14% experienced hallucinations. Longitudinally, hallucinations usually resolve over a period of a few months; although delusions, aggression and other symptoms of agitation tend to be more persistent, with at least 50% of individuals still experiencing these symptoms a year after their onset. Mood symptoms, including depression, anxiety and apathy, are frequent in people with dementia, but are not considered further in this article as there are no indications that treatment with neuroleptics is beneficial.

Several clinico-pathological studies in patients with DLB indicate that there is a significant association between visual hallucinations and loss of choline acetyltransferase (ChAT) from the temporal cortex, which reflects a loss of cholinergic innervation. This association has not been verified in AD, although the results of one study do suggest an association between agitation and loss of ChAT from the frontal cortex in patients with AD. The results of neuropathological studies suggest that the general or regional burden of tangle pathology is a significant
PHARMACOLOGICAL...cont’d

Others...Trazodone, BDZ, Mood stabilizers...
Cyproterone to treat aggressivity in dementia: a clinical case and systematic review

Blanca M Bolea-Alamanac, Simon JC Davies, David M Christmas, Hazel Baxter, Sarah Cullum and David J Nutt

Abstract
Aggressivity is a common problem in the management of elderly patients with dementia. Medications currently used to diminish aggressive behaviour in dementia can have problematic side effects. We present a case and systematic review of the current knowledge about the use of cyproterone acetate to treat aggressivity (excluding hypersexuality related behaviours) in dementia. An 82-year-old man required psychiatric inpatient admission due to agitation and aggressivity and was diagnosed with Alzheimer’s disease. After failed trials of atypical antipsychotics (quetiapine 100 mg/day and risperidone 1 mg/day), drugs for dementia (memantine 20 mg/day and rivastigmine 9 mg/day) and benzodiazepines (lorazepam 0.5–1 mg pm) he was started on cyproterone acetate titrated up to 50 mg twice daily. After two weeks he was calmer and did not express aggressivity. Two months later he was discharged to a community placement where he subsequently remained settled on cyproterone. We reviewed literature on the use of cyproterone in aggressivity (excluding hypersexuality) associated with dementia. We searched the main medical databases including articles in English, Spanish, French and Italian. Only one randomized double-blind trial was found, comparing cyproterone with haloperidol (n = 27). Cyproterone was more effective controlling aggressivity and had lower incidence of side effects. In the one uncontrolled naturalistic observational study identified (n = 19), cyproterone was associated with significant reductions in aggressivity without causing major side effects. Further literature was limited to theoretical discussions. Despite there being evidence to support our observations of a useful role for cyproterone in aggressivity in dementia, further studies are needed to establish the efficacy and safety of this therapeutic option.

Keywords
aggressivity, cyproterone acetate, dementia, violent behaviour
Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial

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IMPORTANCE Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

OBJECTIVE To assess the efficacy, safety, and tolerability of dextromethorphan hydrobromide-quinidine sulfate for Alzheimer disease-related agitation.

DESIGN, SETTING, AND PARTICIPANTS Phase 2 randomized, multicenter, double-blind, placebo-controlled trial using a sequential parallel comparison design with 2 consecutive 5-week treatment stages conducted August 2012-August 2014. Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impressions—Severity agitation score ≥4), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.

INTERVENTIONS In stage 1, 220 patients were randomized in a 3:4 ratio to receive dextromethorphan-quinidine (n = 93) or placebo (n = 127). In stage 2, patients receiving dextromethorphan-quinidine continued; those receiving placebo were stratified by response and rerandomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60).
SUMMARY

- Frequent comorbid debilitating symptoms

- Require a "detective-like" approach with regular adjustment and Team work approach

- Multi-level approach often has the highest success rate
Abstract
Noncognitive neuropsychiatric symptoms (NPS) of dementia (aggression, agitation, depression, anxiety, delusions, hallucinations, apathy, disinhibition) affect individuals with dementia nearly universally across dementia stages and etiologies. NPS are associated with poor outcomes for individuals with dementia and caregivers, including excess morbidity and mortality, greater healthcare use, and earlier nursing home placement, as well as caregiver stress, depression, and difficulty with employment. Although the Food and Drug Administration has not approved pharmacotherapy for NPS, 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. There is evidence of efficacy and limited potential for adverse effects of nonpharmacological treatments, typically considered first line, but their uptake as preferred treatments remains inadequate in real-world clinical settings. Thus, the field currently finds itself in
THANK YOU
Workshop – case presentation

- Case -1
- 80 yo mwf lives with husband, mci
- Admitted with paranoid ideas...?mgt...
Case -2

83yo mwm post eva-probable mixed dementia

Hypersexual, disinhibited behavior

Mgt...
Workshop (cont)

- 69 mwm, lives with his wife,
- Decreased memory, perseverates
- Decreased sleep, wonders at night... mgt