DEMENTIA NEWSLETTER *for* PHYSICIANS

Vol. 4, No. 2 | OTTAWA | Summer 2004

A Publication of the Dementia Network of Ottawa

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An Overview of the Pharmacological Management of Behavioural Disturbances in Dementia

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I am convinced that if you ask any caregiver of a person with dementia what the most challenging aspect of the illness is, they would identify management issues related to the non-cognitive or behavioural and psychological symptoms of dementia (BPSD)[1] as paramount. Rabins' pivotal study 'The Impact of Dementia on the Family' identified that 50 to 90% of caregivers considered physical aggression as the most serious problem they encountered and a factor leading to institutionalization.[2] Similarly, front-line staff working in long-term care report that physical assault contributes to significant work related stress.[3] It is crucial that we have rapid and effective treatments to deal with such potentially dangerous emergency situations which then may allow for proper assessment of underlying problems. Pharmacological treatments also have a place in the treatment of some specific behavioural symptoms when they have not responded to a comprehensive non-pharmacological treatment plan; are distressing, disturbing and persistent for the patient and damaging to their social relationships with others.

Behavioural symptoms associated with Alzheimer disease occur with an estimated prevalence of as high as 90%.[4] A recent study of agitation and its relationship to frontal lobe dysfunction in Alzheimer disease identified that 'agitation' (defined as physical aggression, vocal aggression and active resistance to care on the Neuropsychiatric Inventory (NPI)) never occured in the absence of some other behavioural symptom(s) ie. delusions, disinhibition, irritability and aberrant motor behaviour.[5] BPSD also increase in prevalence with increasing dementia severity**.** This helps to explain why long-term care residents present with such complex behavioural presentations. Therefore, it is unlikely that there will be one umbrella solution that treats all the BPSD

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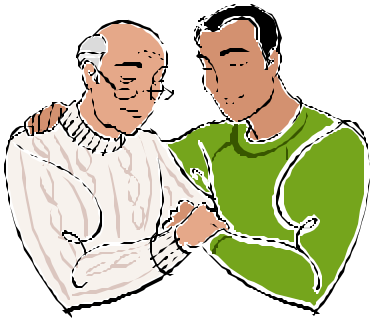
present in a given patient. A comprehensive treatment plan needs to be developed for each symptom.

Management of BPSD involves a thorough medical assessment focusing on identification of the 'target' behavioural symptom(s)[6], its frequency and associated level of distress**.** The goal of assessment is to identify the etiology of the symptom and / or exacerbating conditions. Attention must be paid to the following risk factors: social (i.e. room-mate), environmental (i.e. restraints), intercurrent medical problems (Rule out delirium!), and medication review (removal of potentially offending drugs). BPSD can then be broken down into symptoms that are unlikely to respond to medication including: wandering, hiding, hoarding, eating 'inedibles', inappropriate urination / defecation / dressing / undressing, tugging at / removal of restraints and pushing wheelchair bound co-patients. BPSD that may respond to medication include: sleep disturbances, anxiety / restlessness, withdrawal / apathy, depressive symptoms, manic-like symptoms (elation, hyperactivity, impulsivity) and persistent psychotic symptoms ie. hallucinations / delusions.[7] Diagnostic criteria for depression and psychosis in Alzheimer disease have been developed.[8, 9]

Table 1 summarizes the current treatment strategies using the target symptom approach noted above.

From an evidence-based perspective randomized controlled trials (RCTs) have identified that behavioural symptoms such as psychosis and aggression are most responsive to antipsychotics.[10] The atypical antipsychotics (risperidone, olanzapine and quetiapine) are the best studied and clearly have modest but consistent efficacy in palliating these symptoms. Risperidone is currently the only medication approved in Canada for the treatment of BPSD.[11] These drugs tend to have different side-effect profiles compared to the conventional antipsychotics especially conferring a lower incidence of tardive dyskinesia and EPS. They also come in different formulations which may provide flexibility in administration i.e. quick dissolve and liquid preparations. Although perceived as generally being better tolerated, recent attention has to be paid to certain side-effects of these agents including impact on glucose and lipid metabolism, weight and cerebrovascular events.



The reader is encouraged to review the recent consensus statement on the management of depression and behavioural symptoms associated with dementia.[12] They identify that antidepressants have a role as first line treatments for major depression. Atypical antipsychotics are first line treatments for patients with severe BPSD with psychotic symptoms. The importance of appropriate referral to a mental health professional and multi-disciplinary assessment is highlighted.

Controlled trials have shown that the mood stabilizers (valproic acid, carbamazepine) can be of benefit managing 'agitation'. Other drugs may also have a role in targeting specific symptoms. See Table 1 on page 4.

The cholinesterase inhibitors (ChEIs) donepezil, galantamine and rivastigmine have been shown to have an impact on behavioural symptoms. The data is most robust for those with mild-moderate Alzheimer. Their impact is felt to be modest.[13] Unfortunately studies done to date have not focused on behaviour as a primary measure of outcome and study patients haven't been severely behaviourally disturbed. The NDMA receptor antagonist memantine will soon be available in Canada. Studies in individuals with Alzheimer's already on a ChEI have shown some improvement in global measures of behaviour.

Drugs should be prescribed to meet the needs of the individual taking into account medical co-morbidity and attention to drug-drug interactions. The risk-benefit analysis needs to be agreed upon by a competent patient or their substitute decision maker. The saying "start low and go slow" always applies but make sure that you attempt to achieve a therapeutic trial. Depending on tolerability the dose of some drugs (atypical antipsychotics, antidepressants) can be titrated upward every 3 to 7 days if necessary. A therapeutic trial is approximately 6 weeks.[14] Effectiveness needs to be closely monitored with attention paid to sedation, gait, postural hypotension, cognitive function and other relevant side-effects. Although few in number some studies have shown that discontinuation of psychotropics is possible for some.

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It is suggested that periodic attempts at tapering and discontinuing medication should be made every 6 months after psychotic / aggressive symptoms are stabilized[12].

Pharmacological interventions should not be the treatments of last resort but are an essential part of a comprehensive system of care in the management of BPSD. Future research needs to begin using more precise terminology in order to better identify which interventions: non-pharmacological, pharmacological or both in combination are most appropriate for a given symptom.[10] It has been said that "the treatment of BPSD affords the best opportunity at present for alleviating suffering and societal costs in dementia".[1]

See Table 1 on page 4.

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Table 1: Pharmacotherapies for BPSD

Target symptoms	Medication	Starting dose (mg/day)	Average target dose (mg/day)
· psychosis (delusions, halucinations) · aggression · psychomotor agitation	atypical antipsychotics: · risperidone · olanzapine · quetiapine	0.25 - 0.5 2.5 - 5 12.5 - 25	0.5 - 2 (mean 1) 2.5 - 7.5(mean 5) 50 - 400
· depression · anxiety · irritability	antidepressants: · citalopram · sertraline · mirtazapine · venlafaxine · trazodone (with sleep disturbance)	10 25 15 37.5 10 - 25	10 - 40 50 - 100 15 - 45 37.5 - 150 50 - 100
· sleep-cycle disturbances · anxiety states (short term use) · anxiety in predictable situations (premedication)	anxiolytics: · lorazepam · oxazepam · zopiclone (for insomnia)	0.5 - 1 5 - 10 3.75	1.5 - 2 10 - 30 3.75 - 7.5
· impulsivity · mood lability · disinhibition	mood stabilizers: · valproic acid · carbamazepine	250 50 - 100	400 - 1,000 300 - 800

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The Dementia Network of Ottawa would like to thank Novartis, Janssen-Ortho, and Pfizer for sponsoring this edition of the Dementia Newsletter for Physicians.

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