From Transmitters to Treatment: The Pharmacotherapy of Behavioural Disturbances in Dementia

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Background: Behavioural disturbances in dementia are a common cause of excess morbidity, impairing the quality of life for both patient and caregiver. As part of a comprehensive approach to management, which includes a search for underlying causes and behavioural interventions, pharmacotherapy can be extremely helpful in alleviating symptoms such as agitation, aggression, and psychosis.

Method: This paper reviews recent studies that examine the neurochemical basis of these behavioural disturbances in order to provide a rationale for the various classes of psychotropics which have been used.

Results: While neuroleptics have been the best-studied class of drugs to date, modest efficacy and significant potential side effects often limit their use. Newer atypical neuroleptics may be better tolerated, though controlled data have yet to be published. There is increasing support for the use of carbamazepine and antidepressants such as trazodone and the selective serotonin reuptake inhibitors (SSRIs).

Conclusion: Further controlled studies of all of these agents are required in order to determine whether transmitter-specific or behaviour-specific targeted interventions truly provide a rationale for the effective pharmacotherapy of these disorders.

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Key Words: dementia, behavioural disturbances, pharmacotherapy

Behavioural disorders associated with dementia (BDD) have only recently been identified as an important focus for research and treatment. Diagnostic classification systems and diagnostic instruments for dementia have characteristically relied on intellectual impairment to define this disorder. In fact, DSM-III-R (1) criteria for dementia listed “personality change” as the only behavioural disturbance associated with this disorder, while the DSM-IV (2) and the National Institute of Neurological and Communicative Disorders and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (3) criteria do not include any behavioural disturbances (although these are specifiers for subcoding with DSM-IV and are included as factors that support and/or are consistent with the diagnosis in the NINCDS-ADRDA criteria). Despite this emphasis on the “cognitive paradigm” (4), behavioural disturbances such as apathy, depression, euphoria, and psychosis were historically recognized by Alzheimer in his initial description of the illness (5), and numerous studies have documented that these disturbances are serious problems which significantly affect the quality of life for both patient and caregiver. In one of the earliest studies in this area, Rabins and others (6) interviewed primary caregivers of patients suffering from irreversible dementia and found behavioural disturbances such as catastrophic reactions, critical behaviour, wandering, accusations, delusions, and hallucinations occurred in approximately 50% to 90% of patients. They also noted that physical violence was rated most frequently as a serious problem, even more frequently than the memory disturbance. Other studies have shown that even modest improvement in these behaviours can result in significant improvement in the quality of life.
life, although it is these behaviours that often result in the institutionalization of the demented elderly (7,8).

Behavioural disturbances have been defined as “alterations in perceptual and cognitive functions, psychomotor performance, motivations, mood, interpersonal relationships, or intrapsychic processes of a person to the degree that they interfere with or limit the capacity of the individual to function within his/her setting, or constitute a hazard to his/her physical well-being” (9, p 127). BDD-specific symptoms include disruptive, agitated behaviours, psychotic behaviours (delusions, hallucinations), wandering and other activity disturbances, aggression, uncooperativeness, diurnal rhythm disturbances, affective disturbances, anxiety, phobias, and sexual inappropriateness (10–13). The phenomenology and prevalence of these disturbances have been noted in previous studies (14–19). For example, disruptive behaviours are common and occur in at least 40% of patients with Alzheimer’s disease (AD) at some point during the course of their illness (20), though prevalence estimates have varied up to 90% (21). Of nursing home residents, 36% to 64% exhibit some form of BDD (22–24), at least 50% of outpatients treated in dementia clinics experience BDD (15,25), and more than 50% of patients cared for at home have been noted to experience agitation (25). Despite the prevalence and seriousness of these disorders, it was only recently that a multidisciplinary task force convened by the United States Alzheimer’s Association identified the assessment and treatment of behavioural problems as a first priority for research (21).

The Neurochemical Basis of Behavioural Disorders

Neuronal System Dysfunction in Dementia

There is mounting evidence that links BDD to specific alterations in neurochemistry, which may provide the basis for pharmacological manipulations. AD is associated with dysfunction in multiple neurotransmitter systems. Although the most well-studied neuronal system dysfunction is in the cholinergic system, there is also evidence supporting dysfunction in the serotonergic, noradrenergic, dopaminergic, and γ-aminobutyric acid (GABA) systems (26–28). Since these neurotransmitters are known to regulate behaviours and are also amenable to pharmacologic intervention, research attention has recently focussed on the possible relationship between these neurotransmitter dysfunctions and the behavioural disorders seen in dementia.

Serotonin (5-hydroxytryptamine [5-HT])

Evidence has now accumulated that supports the existence of a significant serotonergic deficit in AD (29). This includes loss of neurons in the raphe nuclei, postmortem brain studies showing decreased concentrations of 5-HT and 5-hydroxyindolacetic acid (5-HIAA) in the central nervous system, particularly the temporal cortex, and significant losses of 5-HT₁ and 5-HT₂ receptors in the cortex, hippocampus, and amygdala of AD patients (5-HT₁-s unknown) (27,30–33).

Serotonergic projections from the raphe nuclei are widespread and innervate many structures in the cortex and limbic system (30). This neurotransmitter is involved in the regulation of many psychobiological functions such as mood, feeding behaviour, sleep, temperature, and sexual and motor activity and generally plays an inhibitory role on motivated behaviour and on other neurotransmitter systems (30,34). Alterations in the functioning of the central serotonergic system, therefore, can be expected to affect many different types of behaviour.

Postmortem studies have shown that decreased levels of 5-HT may be related to specific behaviours in patients with AD. Zubenko and others (35) found decreased levels of 5-HT in some areas of the brain in AD patients with psychotic behaviours compared with AD patients without psychosis. A second postmortem study demonstrated that patients with a history of agitation and aggression prior to death had decreased cortical levels of 5-HT compared with nonagitated patients (36). These findings were not replicated in another study looking at the temporal cortex and both psychotic and nonpsychotic symptoms in patients with AD (37). A recent study by Chen and others (38) showed that chronic neuroleptic treatment was associated with significant reductions in the concentration of 5-HT in the frontal cortex and 5-HIAA in the temporal cortex. Whether this finding is related to behaviour or to treatment with neuroleptics is unclear. Chen and others’ study highlights the importance of controlling for confounding factors such as medication use.

5-HT has also been related to behavioural disorders in clinical studies by examining cerebrospinal fluid (CSF) levels of the 5-HT metabolite 5-HIAA and peripheral markers. Levels of 5-HIAA in CSF have been positively correlated with some items of emotional impairment, in particular, anxiety and fear or panic (39). Schneider and others (40) evaluated the relationship between markers of serotonergic activity and behavioural disorders in patients with AD, predominantly agitation and delusions. The agitated/delusional groups showed significantly lower peripheral serotonergic activity (as measured by binding to the platelet 5-HT transporter system) than uncomplicated AD subjects or controls. Since depressed patients were not excluded and depression is a common feature of AD, however, this result may also reflect the presence of comorbid depression in some of these patients. In support of this hypothesis, a previous report found no differences in platelet maximum number of binding sites (Bₘₐₓ) between 9 AD patients and 11 age-appropriate controls when subjects with depressive symptoms had been excluded. Furthermore, a negative correlation has been found between CSF 5-HIAA and platelet 5-HT₂ receptor indexes in other...
neuropsychiatric patients (41), indicating that this peripheral marker may not reflect the central serotonergic system.

In a neuroendocrine study in dementia by Lawlor and collaborators (26), the 5-HT agonist m-chlorophenylpiperazine (m-CPP) was administered intravenously to 12 patients with AD and 10 age-matched controls. Patients with AD showed increased behavioural responsiveness (psychomotor activation, restlessness, and perceptual abnormalities) compared with controls (26,42). This finding may reflect damage to the serotonergic system with compensatory upregulation of the remaining postsynaptic receptors (30). Surprisingly, there were no differences in neuroendocrine response to m-CPP; both groups showed significant and similar increases in plasma prolactin and cortisol levels. In vitro studies, however, show that m-CPP binds to 5-HT$_{1A,B}$, 5-HT$_2$, and 5-HT$_3$, as well as to $\alpha_1$, $\alpha_2$, $\beta$-adrenergic, dopaminergic, and cholinergic sites. Although there are significant discrepancies between these binding site data and the results of pharmacological studies in vivo, it is possible that some of the effects of m-CPP are due to actions at nonserotonergic neuronal systems. Furthermore, there was no assessment of behavioural disorders in these patients. Other studies have demonstrated a neuroendocrine hyperresponsivity in AD, although no attempt was made to relate this to behavioural disturbances (43). Disruptions in serotonergic functioning have also been associated with depressive symptoms (38) and anxiety (44). In summary, there is fairly strong evidence relating serotonergic dysfunction to a variety of agitated and psychotic behaviours, although early studies did not control for neuroleptic exposure.

Norepinephrine (NE)

Postmortem studies have consistently shown involvement of the noradrenergic system in the AD process, with decreased NE levels being demonstrated in many brain areas (27,31–33,35,45). Changes in the locus coeruleus, the major source of NE in the brain, have been demonstrated in AD patients (46,47). These changes are not reflected in the CSF of patients (45,48).

Animal studies have shown the NE neurons from the locus coeruleus are involved in the sleep–wake cycle, levels of vigilance, and emotion (49). Lesions to the locus coeruleus have been demonstrated in many disorders including Parkinson’s disease, paranoid schizophrenia, and a form of endogenous depression (49). Thus there is reason to suspect that dysfunction in the NE system may play a role in BDD. Postmortem studies have shown that AD patients with psychotic behaviours and agitation have higher levels of NE than those AD patients without these behaviours. Zubenko and others (35) found that psychotic AD patients had significantly increased NE levels in the substantia nigra, with trends toward higher levels in other areas. The higher levels of NE in patients with psychotic symptoms are comparable to NE levels in the brains of elderly nondemented control subjects, suggesting that NE levels are preserved rather than increased with psychosis (50). For agitation, the evidence is less clear. Although restlessness has been related to CSF levels of the NE metabolite 3,4-methoxy-5-hydroxy-phenylglycol (MHPG) in patients with AD (39), CSF levels of MHPG are also known to increase with advancing disease (51). A subsequent study has replicated the finding of increasing MHPG with increasing cognitive decline, but those investigators found that correlations between plasma MHPG and agitation and psychotic behaviours were not significant (52).

AD patients who showed depressive symptoms prior to death demonstrated significantly greater neuronal loss in the locus coeruleus than patients without such symptoms (49,53–55). These findings are also supported by postmortem studies showing that demented patients with depression have significantly lower levels of NE than those without depression (50). Clinical studies have also demonstrated that markers of NE dysfunction are increased in AD patients with depression compared with those without depression (56). Thus depressive symptoms in AD may be related to deficits in the noradrenergic system.

Dopamine (DA)

Postmortem studies have demonstrated disruptions in the dopaminergic system in patients with AD compared with controls (27,32), although it is less affected than other biogenic amines (31). A positron emission tomography study of patients with dementia demonstrated that disruptions in DA metabolism became increasingly severe as the cognitive impairment progressed (57). Although dopaminergic dysfunction has been implicated in depression, agitation, and psychosis in nondemented patients, the clinical correlates of DA dysfunction in AD patients have yet to be shown. Zubenko and others (35) found that there were no differences in levels of DA or its metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in either cortical or subcortical regions in AD patients with psychotic versus nonpsychotic behaviours. Bierer and others (58) replicated the lack of a correlation between indicators of dopaminergic neurotransmission and the presence of psychosis and also demonstrated that there was no relation with depression or agitation. Sweet and others (59) showed that demented patients with psychosis had 2 distinct levels of dopaminergic functioning as demonstrated by prolactin response to neuroleptic challenge. While this finding may be a result of differing levels of cognitive impairment, it may have implications for neuroleptic response. Although no association has been found between the DA system and behavioural disorders in AD and other dementias, there is a paucity of studies addressing this issue.
GABA

The neurotransmitter GABA is reported to be involved in behaviours such as aggression. Animal studies have shown that increasing GABA can decrease aggression (60). Deficits in the central GABA system have been demonstrated in the brains of patients with AD (61,62). Although there are no clinical studies linking changes in the GABA system with particular behaviours seen in AD, some indirect evidence is provided by some of the drugs that are effective in the treatment of agitation. Benzodiazepines are thought to exert their effects by potentiating GABA transmission. Furthermore, valproic acid, which is also effective in aggressive behaviours associated with AD, is also believed to increase GABA (63). Clearly, direct evidence is required before any link between disruptions in the GABA system and specific behaviours is demonstrable.

Acetylcholine

In AD, neurochemical and neuropathological degenerative findings in the central cholinergic neurons are consistently reported. Pathological studies show profound changes in the major cholinergic system arising in the basal forebrain and projecting to the cortex (47,64–66). Autopsy studies consistently demonstrate marked and widespread decreases in the cholinergic markers choline acetyltransferase and acetylcholinesterase in the cortex, particularly the temporal cortex (33,67–69). A significant loss of neurons in the nucleus basalis of Meynert was reported in patients with AD when compared with age-matched controls (64,70). In studies in which AD patients and age-matched control subjects were compared, it appears that the muscarinic type II (M2) presynaptic receptor density is also reduced in AD (65,69).

Cholinergic neurons arise in the basal forebrain (nucleus basalis of Meynert, diagonal band of Broca, and the medial septum) and innervate the cortex, including the hippocampus and a variety of subcortical structures. The nucleus basalis of Meynert contains a high percentage of cholinergic neurons and projects to widespread areas of the cortex. Alterations in the central cholinergic system, therefore, can be expected to cause significant disruptions in the functioning of the neocortex. The importance of brain cholinergic neurons in cognition have long been known (71–77), but there is only weak evidence suggesting that this neurotransmitter plays an important role in the noncognitive disorders associated with dementia. Only 2 postmortem studies were found that provide some evidence that neuronal loss in the nucleus basalis or decreases in cholinergic transmission are correlated to psychotic symptoms in some forms of dementia (78,79).

In summary, there is substantial evidence showing that AD and other dementias are associated with widespread changes in many neurotransmitter systems. Attempts have been made to link these individual neurotransmitter dysregulations with specific behaviours. The strongest evidence links the serotonergic and noradrenergic systems with noncognitive disorders. Much of this evidence is based on postmortem studies looking at neuronal counts and levels of neurotransmitters and their metabolites as well as clinical studies looking at the presence of metabolites in the CSF. Results from these types of studies must be interpreted with caution. The strongest postmortem studies are those in which antemortem prospective data collection has been done. Behavioural disorders are difficult to define, and standardized instruments should be used to monitor behaviours over time. Furthermore, different behaviours may or may not be present immediately preceding death, so some behaviours may be a state rather than a trait phenomenon. This makes it necessary to keep the time between clinical assessments and postmortem assessments short. Different behaviours peak in intensity at different times during the ongoing cognitive decline (80), meaning the severity of the cognitive decline may also affect our ability to detect certain neurotransmitter abnormalities. Medication use can have a significant effect on both postmortem and clinical CSF studies. Many of the postmortem studies do not account for medication use, which makes the interpretation of results difficult. Clinical studies looking at plasma and CSF neurochemical markers avoid problems with time delay but must also account for medication use at the time of study. These studies examine a surrogate measure of central function that may or may not be accurate.

It is fairly clear that neurotransmitter abnormalities are probably involved in the changes in behaviour seen in AD and other dementias. Based on such a paradigm, the pharmacological interventions that will be reviewed next could theoretically be organized by the major neurotransmitter class upon which they are presumed to act: DA (for example, neuroleptics), NE (for example, ß-blockers, monoamine oxidase inhibitors [MAOI], and tricyclic antidepressants), 5-HT (for example, SSRIs, buspirone, ondansetron), GABA (for example, benzodiazepines, valproic acid), and acetylcholine (for example, tacrine, physostigmine). Unfortunately, such a simplistic approach ignores the fact that the different types of behavioural disorders tend to coexist in dementia rather than occur in isolation. For example, in studies looking at psychotic behaviours, many of the patients probably exhibited concomitant nonpsychotic behaviours. Furthermore, the control of each behaviour is likely achieved through the intricate balance of many neurotransmitter systems. Thus it is not surprising that each neurotransmitter has been associated with various overlapping behavioural subtypes. Even though these studies have looked at isolated neurotransmitters, the activity of one neurotransmitter cannot be clearly separated from the activity of another. For example, 5-HT is a cotransmitter with GABA and NE, and serotonergic neurons from the raphe nucleus inhibit noradrenergic neurons in the locus coeruleus (81). Although the control of behaviour is complex, the careful study of the patterns of behaviour linked to each of
the neurotransmitter abnormalities may still yield information that would allow pharmacotherapeutic interventions to correct neurotransmitter imbalances which would be patient- and state-specific.

Management of BDD

The management of BDD should always begin with an assessment of any change in behaviour, including a detailed assessment of the patient’s medical status and environment. Underlying medical conditions must be treated if infection or pain results in a concomitant delirium. Numerous medications have been associated with BDD, and these should be reduced or discontinued. Other stimuli that could cause or exacerbate BDD should also be considered, for example, hunger, cold, constipation, and environmental misperceptions as a result of changes in vision or hearing. The amelioration of many of these conditions can often lead to significant improvements in BDD. Finally, a detailed assessment of the patient’s environment and the context in which these behaviours occur is the first step in designing a behavioural management plan for these disorders. While a detailed description of the nonpharmacological management of BDD is beyond the scope of this review, these interventions should be considered prior to resorting to pharmacological approaches (10,82,83). Nonpharmacological approaches include behaviour management (84,85), environmental modifications, interventions using sound and light, social interaction, and other psychosocial activities (86).

Although the treatment of BDD requires biological, psychological, and social interventions, drug utilization studies in elderly patients have shown that psychotropic medications are frequently used in hospitals (87), long-term care facilities (88–90), and the community (91). There has been growing concern that these medications are overused, misused, and administered by staff who have little understanding of their risks and benefits (88). Such concerns resulted in the United States Omnibus Reconciliation Act (OBRA-87) guidelines, which describe the appropriate use of such medications (92,93).

Neuroleptics

The most commonly used and by far the best-studied pharmacological intervention for BDD is neuroleptic medication (10,94–96) (Table 1). In a metaanalysis of controlled trials of neuroleptics that included papers published from 1966 to 1989, Schneider and others noted that neuroleptics changed the improvement rate from 41% to 59% compared with placebo (97). Besides asserting this “modest” efficacy, they also concluded that no single neuroleptic was better than another. Since 1989, there have been surprisingly few studies of typical neuroleptics. A single-blind study of 9 AD patients treated with haloperidol 1 to 5 mg/day demonstrated improvements in behavioural ratings but also significant treatment-emergent extrapyramidal symptoms, as well as a decline in cognitive function (98). In a double-blind comparison of zuclopenthixol and thioridazine, Harenko and others (99) noted equally significant improvements in both groups, the only significant difference being a better effect of zuclopenthixol on sleep disturbance. This study replicated the somewhat surprising previous findings (97) that the low-potency, highly anticholinergic neuroleptics, such as thioridazine, do not appear to cause more side effects than higher-potency neuroleptics. In another double-blind comparison of loxapine (a mid-potency neuroleptic) and haloperidol (a high-potency neuroleptic), efficacy was equally significant in both groups, though haloperidol treatment resulted in significantly more side effects than loxapine (100). Finally, in the only recent double-blind, randomized, placebo-controlled trial, the use of thiothixene was examined in 36 agitated and demented nursing home patients (101). Treatment with thiothixene was associated with significantly greater reductions in agitation scores, with 65% of thiothixene-treated patients rated as significantly improved compared with only 19% of placebo-treated patients. Furthermore, except for sedation, there were no differences in treatment-emergent side effects.

Table 1. Selected antipsychotics studied for the treatment of BDDa

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Dose (mg/day)b</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical neuroleptics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliphatic phenothiazine</td>
<td>Chlorpromazine</td>
<td>10 to 200</td>
<td>Sedating; significant anticholinergic symptoms and postural hypotension</td>
</tr>
<tr>
<td>Piperazine phenothiazine</td>
<td>Trifluoperazine</td>
<td>1 to 15</td>
<td>Significant extrapyramidal symptoms</td>
</tr>
<tr>
<td>Piperidine phenothiazine</td>
<td>Thoridazine</td>
<td>10 to 200</td>
<td>Sedating; significant anticholinergic symptoms and postural hypotension</td>
</tr>
<tr>
<td>Thioxanthene</td>
<td>Thiothixene</td>
<td>1 to 15</td>
<td>—</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>Haloperidol</td>
<td>0.25 to 4</td>
<td>Significant extrapyramidal symptoms</td>
</tr>
<tr>
<td>Dibenzodiazepine</td>
<td>Loxapine</td>
<td>5 to 50</td>
<td>—</td>
</tr>
<tr>
<td>Atypical neurolepticsc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dibenzodiazepine</td>
<td>Clozapine</td>
<td>6.25 to 200</td>
<td>Sedating; significant anticholinergic symptoms and postural hypotension</td>
</tr>
<tr>
<td>Benzisoxazole</td>
<td>Risperidone</td>
<td>0.25 to 2</td>
<td>Orthostatic hypotension</td>
</tr>
</tbody>
</table>

a Table modified from Herrmann and others (96).
b Approximate dose; upper limits of recommended dosage ranges have not been well established.
c Studied in open-label trials only.
While these data consistently support the modest efficacy of traditional neuroleptics for BDD, concern still exists about potential side effects, especially extrapyramidal symptoms. This concern was highlighted in a recently published study that prospectively compared the development of perphenazine-induced Parkinsonism in a group of elderly patients with major depressive disorder and psychosis with a group of AD and BDD patients (102). While the group with depression did not experience an increase in Parkinsonism, the patients with AD doubled those scores on a standardized extrapyramidal symptom rating scale, despite receiving half the dose of perphenazine and having briefer exposure. These findings have led to increased interest in the use of atypical antipsychotic agents.

Atypical antipsychotics offer significant theoretical advantages over standard neuroleptics because of a reduced potential to cause extrapyramidal symptoms in this highly vulnerable population. Unfortunately, there have been no controlled trials to date of any of the currently marketed atypical antipsychotics, including clozapine, risperidone, and olanzapine. The use of clozapine for the treatment of BDD was described in a retrospective series of 18 elderly inpatients, 16 of whom had moderate or severe dementia (103). Most patients tolerated the medication at doses ranging from 12.5 to 200 mg/day. By contrast, in a small series involving 4 elderly patients, 3 of whom had moderate to severe dementia, only 2 patients responded, and all 4 experienced significant adverse events including falls, bradycardia, and delirium (104). The dosages used in this study ranged from 6.25 to 37.5 mg/day. Additional concerns regarding the tolerability of clozapine were noted in a retrospective chart review of 20 elderly patients. In this series, 16.7% of patients treated with clozapine developed leukopenia, a substantially higher incidence than the rate of agranulocytosis reported in mixed-age samples (105). Furthermore, pharmacokinetic and pharmacodynamic changes predict an increase in expected adverse effects of clozapine in the elderly (106). Thus the safety and efficacy of clozapine for BDD require further documentation.

Remoxipride, a selective D2 receptor antagonist, demonstrated a good effect on psychomotor hyperactivity in 81% of 103 elderly patients with dementia or delirium (107). Remoxipride also decreased Brief Psychiatric Rating Scale scores and reduced psychotonic symptoms in 8 of 9 Parkinson’s disease patients, with only 2 patients demonstrating a slight decrease in motor performance (108). Unfortunately, remoxipride has been withdrawn from the market because of an association with aplastic anemia.

There is a small amount of anecdotal literature on the use of risperidone for the treatment of BDD. Compared with clozapine, risperidone theoretically offers the advantages of less anticholinergic symptoms and far less sedation—2 important features to be considered in the treatment of BDD. In a study of 9 elderly inpatients with BDD, 7 patients showed significant decreases in scores on a behavioural rating scale, while 2 dropped out because of lack of efficacy (109). In a small case series of 11 geriatric inpatients (3 of whom appeared to have BDD), marked improvement with risperidone treatment was noted, despite adverse events that included orthostatic hypotension, dizziness, abdominal cramps, headache, somnolence, and hypotension (110). Risperidone has recently been suggested for use in the treatment of BDD in Lewy body dementia. In a single-case report, Lee and others (111) noted improvement in paranoia, hallucinations, and agitation in a 74-year-old patient with Lewy body dementia treated with 2 mg of risperidone. Allen and others (112) described 3 patients with Lewy body dementia whose psychosis and agitation improved with risperidone 0.5 mg once or twice daily. None of their patients experienced a decline in cognition, a concern noted in treatment with some typical neuroleptics.

In the treatment of psychosis and behavioural disturbances associated with Parkinson’s disease, 2 studies have reported different experiences. Rich and others (113) noted improvement in only one patient, while 5 of 6 experienced “intolerable” exacerbations of Parkinsonism. The doses of risperidone used in the study ranged from 2 to 4 mg/day (average 2.2 mg/day). In contrast, a study by Meco and others (114) noted significant improvement in hallucinations and Brief Psychiatric Rating Scale scores in a group of 6 Parkinson’s disease patients without any worsening of cognition and motor symptoms. The range of doses of risperidone in their study was 0.25 to 1.25 mg/day, far lower than the previous study. Clinical recommendations for elderly patients with schizophrenia suggest a maximum daily dose of 2 mg (115), but these results suggest that even lower dosages should be considered in patients with dementia, particularly in patients with Parkinsonism. Although these preliminary studies suggest that low doses of risperidone may be a viable alternative to typical neuroleptics, controlled trials are urgently needed.

β-Blockers

Based on their use in the treatment of aggression and violence in brain-damaged patients (116), propranolol and pindolol have been studied in several case series and controlled trials for their potential use in the treatment of aggression and agitation in dementia (117–122). Unfortunately, these trials used crossover designs and involved small numbers of mixed-age patients with a variety of diagnoses (119–121). A recent review of these studies suggested that drug responses from double-blind, placebo-controlled trials were 67% (123). The dosages of β-blockers that have been used to treat BDD greatly exceed the recommended dose for cardiovascular indications (Table 2). Studies have typically used 200 to 800 mg/day of propranolol (124) and 40 to 60 mg/day of pindolol (120). While improvement can occur between 2 and
4 weeks (123), treatment with the highest dose tolerated for a minimum of 8 weeks is necessary in order to determine efficacy (124). By contrast, a recent report on 12 aggressive, agitated dementia patients suggested that low-dose propranolol (10 to 80 mg/day) was effective in 67% of patients in as little as 2 weeks from initiation of treatment (125).

**Lithium Carbonate**

While lithium has been shown to reduce agitation and aggression in mixed-age patients with mental retardation (123) and aggressive prisoner populations (126), there are no controlled trials of this medication for BDD. In their review of nonneuroleptic medications for BDD, Schneider and Sobin (127) noted that of 22 published cases of AD patients treated with lithium, only 4 patients were noted to have improved. A potential criticism of these case reports, however, is that many of these patients were treated with extremely low doses and may therefore not have reached the relatively high serum concentrations recommended for the treatment of BDD (124). While there is currently little evidence to recommend the use of lithium for BDD, some authors suggest that it should be used in dementia patients who have a significant affective component to their symptoms (128).

**Benzodiazepines**

One of the first medications to undergo controlled trials for the treatment of BDD was the benzodiazepine class. Three large studies published in 1965 compared oxazepam with placebo in over 300 elderly patients (129–131). While these studies did not use diagnostic criteria or rating scales and included patients with mixed diagnoses, many of these patients may have fulfilled current diagnostic criteria for dementia. All 3 studies showed significantly more improvement with the benzodiazepine than with placebo.

Several more recent studies have compared the efficacy of benzodiazepines with that of neuroleptics (132–135). Coccaro and others (135) compared haloperidol, oxazepam, and diphenhydramine in 59 patients with dementia in an 8-week, randomized, double-blind study. While all 3 treatment groups improved significantly, there was a trend toward greater improvement with the antipsychotic compared with the benzodiazepine.

Recommendations have generally emphasized the use of short-acting benzodiazepines for use in BDD (84,124,136). In contrast, several case reports have described the use of clonazepam, a long half-life benzodiazepine, for the treatment of BDD (137–139). Clonazepam appears to increase 5-HT levels directly, unlike other benzodiazepines, and may therefore have a more specific action than sedation. Regrettably, there are no controlled trials to date using this medication. A recent review concluded that the short-term use of short-half-life benzodiazepines is effective for BDD (136). Concerns remain, however, because of the potential for tolerance to develop with long-term use, side effects, and drug interactions, as well as the possibility that they may not be as effective as agents such as neuroleptics.

**Antidepressants**

There has recently been a greater focus on the use of antidepressants to treat BDD. Agents such as the tricyclics, the heterocyclics (for example, trazodone), SSRIs, and MAOIs have all been used for various indications. The foci of many of these studies have included their effects on cognition, agitation, aggression, and depression.

In the first double-blind, placebo-controlled trial of an antidepressant for the treatment of depression in AD, Reifler and others (140) examined the effects of imipramine. While there was a marked improvement in depression scale scores in patients treated with imipramine, the placebo group improved to the same degree. The authors concluded that their results indicated only that depressive symptoms in AD responded to treatment because patients in both groups received potentially beneficial interventions, including supportive vis-

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**Table 2. Selected nonneuroleptic medications for the treatment of BDD**

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<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterocyclic antidepressants</td>
<td>Trazodone</td>
<td>25 to 300</td>
<td>Use divided doses; possible sedation and orthostatic hypotension</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Fluoxetine</td>
<td>5 to 20</td>
<td>Possible gastrointestinal side effects including nausea, diarrhea, and weight loss</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>25 to 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>10 to 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>50 to 100</td>
<td></td>
</tr>
<tr>
<td>MAOIs</td>
<td>Moclobemide</td>
<td>300 to 450</td>
<td>Studied for use in dementia with depression only</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>100 to 800</td>
<td>Adjust dosage for serum levels 4 to 8 µg/mL.; possible sedation, gait unsteadiness</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Propranolol</td>
<td>10 to 240</td>
<td>May require 8 weeks for effect; possible bradycardia and hypotension</td>
</tr>
<tr>
<td></td>
<td>Pindolol</td>
<td>10 to 60</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam</td>
<td>0.5 to 3</td>
<td>Possible sedation, falls, tolerance, withdrawal reactions</td>
</tr>
<tr>
<td></td>
<td>Oxazepam</td>
<td>10 to 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>0.5 to 1.5</td>
<td></td>
</tr>
<tr>
<td>Azapirones</td>
<td>Buspirone</td>
<td>10 to 45</td>
<td>Possible nausea</td>
</tr>
</tbody>
</table>

*a Table modified from Herrmann and others (96).

*b Approximate dose; upper limits of recommended dosage ranges have not been well established.
its with the study physicians and nurse coordinators. In this study, imipramine, which is a tertiary amine tricyclic antidepressant, was extremely well tolerated, with no differences in experienced adverse effects or cognitive function compared with placebo. Similarly, doxepin, another tertiary amine, was found to be effective and well tolerated for treating 6 “noisy” patients with dementia and depressive symptoms (141). These 2 reports would appear to contrast clinical recommendations about avoiding the use of tertiary amines in this population (83). Caution, however, might still be required based on a more recent study with another tertiary amine, clomipramine. In this small, double-blind, controlled crossover study, clomipramine was significantly more effective than placebo at treating depression in a group of AD patients (142). All patients in the active-drug subgroup experienced side effects such as dry mouth, dizziness, and sleep difficulties. Furthermore, patients treated with clomipramine showed a small but significant lowering of Mini-Mental State Examination scores compared with the placebo group.

The use of trazodone for the treatment of BDD has received increasing attention. Summarizing the early case reports on the use of trazodone, Schneider and Sobin (127) noted that on doses of 150 to 500 mg/day, 9 of 23 dementia patients were judged to have improved. Adverse effects, including sedation and orthostatic hypotension, however, were noted to be quite common. More recently, several naturalistic, open-label trials and case series, as well as one small, placebo-controlled trial, have been published. In 2 uncontrolled trials (143,144) with 38 dementia patients, 84% experienced at least mild improvement, and 32% were described as markedly improved on average daily doses of approximately 175 mg. In 2 other series (145,146) that used much smaller doses (25 mg 3 times daily or 50 mg at bedtime), 15 patients with BDD were described as having experienced significant decreases in emotional lability, irritability, anxiety, restlessness, and agitation. In the only placebo-controlled trial to date (147), 10 patients with AD received either trazodone (maximum 50 mg 3 times daily), buspirone, or placebo in a double-blind crossover trial. Patients receiving trazodone had small but significant improvements compared with placebo and buspirone, though some could not tolerate 150 mg/day because of excessive sedation. In summary, while there are many reports of the safety and efficacy of trazodone for BDD, only one controlled trial to date has demonstrated modest improvement and tolerability.

Use of SSRIs for BDD has been documented with both anecdotal data and controlled trials. In a case series describing the use of fluoxetine in 10 patients with AD, mood lability, irritability, anxiety, and fear significantly improved (148). Fluoxetine was well tolerated, with the only adverse effect of appetite loss in one patient. By contrast, however, another series of 5 patients treated with fluoxetine experienced no improvement on any measure of cognition or behaviour and a high incidence of adverse effects such as confusion, agitation, dizziness, nausea, anorexia, weight loss, and insomnia (149).

In a large, well-designed, double-blind, placebo-controlled trial, Nyth and Gottfries (150) studied the effects of citalopram in 98 dementia patients. Significant improvements in emotional bluntedness, confusion, irritability, anxiety, fear, depressed mood, and restlessness were noted in the citalopram group but not in the placebo group. In another double-blind, controlled trial comparing fluvoxamine with placebo in 46 patients with dementia, Offfson and others (151) could document only trends favouring the antidepressant. Though both placebo-controlled trials suggest that SSRIs may be effective in managing behavioural disorders, studies of their effectiveness in severely disturbed patients with BDD are still required.

Early interest in the use of traditional MAOIs was raised by a case report of 2 demented patients with depression treated with tranylcypromine (152), but no further clinical experience or studies have been described. More recently, interest has shifted to the newer selective MAO-A and MAO-B inhibitors. Based on the presence of NE lesions in senile dementia of the Alzheimer type and the ability of moclobemide, a selective MAO-A inhibitor, to reverse scopolamine-induced cognitive deficits (153,154), this agent has recently undergone a trial in demented patients with depression. Roth and others (155) studied 511 patients with dementia and depressive symptoms, as well as 183 patients with depression and cognitive impairment in a double-blind, placebo-controlled trial with a fixed dose of moclobemide 400 mg/day. Both groups of patients experienced significantly more reductions in their Hamilton Depression Rating Scale scores over 6 weeks compared with placebo, with patients in the dementia group also experiencing a slight but significant increase in Mini-Mental State Examination scores as well. Caution is required when interpreting these results, however, because another double-blind, placebo-controlled trial in elderly depressive patients without dementia did not demonstrate efficacy better than placebo when using the same fixed-dose strategy of 400 mg/day (156).

Selegeline is a selective MAO-B inhibitor when used at low dosages (10 mg/day). While a recent study has demonstrated antidepressant efficacy in the elderly (157), it is currently marketed only for the treatment of motor manifestations of Parkinson’s disease. A number of case series have suggested modest improvements in some measures of behaviour using selegiline (158–160). Several double-blind, placebo-controlled trials have shown mild but significant reductions in BDD (161,162). In a recent randomized, double-blind, placebo-controlled parallel study, Burke and others (163) demonstrated a slight but significant improvement on a single measure of behaviour in 39 patients.
Controlled trials with more severely disturbed patients are still required.

**Anticonvulsants**

The use of carbamazepine for the treatment of BDD has now been described in several case reports, case series, open-label trials, and 3 controlled trials. In the uncontrolled trials, carbamazepine in doses of 100 to 1000 mg/day had a high rate of response within 2 to 4 weeks and was extremely well tolerated (164–168).

In the first double-blind, placebo-controlled study, 19 patients with dementia were treated with carbamazepine 100 to 300 mg/day (169). The study failed to demonstrate any significant placebo–drug differences, but numerous methodological problems, including a crossover design, small numbers, lack of inclusion/exclusion criteria, use of low dosages and serum concentrations, and low baseline frequency of aggression, could have accounted for the negative outcome.

In contrast, 2 recent placebo-controlled studies suggested much more positive results. In one, a crossover study of 25 demented nursing home residents treated with carbamazepine 100 to 800 mg/day, there were significant decreases in overall psychopathology compared with placebo (170). Seventy percent of carbamazepine-treated patients were rated as improved versus only 17% on placebo. In the other study, the aggressive behaviour of 6 patients wors significantly reduced with carbamazepine in doses of 200 to 600 mg/day (171). In summary, while there is significant anecdotal evidence supporting the use of carbamazepine for BDD, the controlled studies are small and demonstrate conflicting results. Clinically, recommendations have included attempting to individualize the dosage to achieve serum concentrations of approximately 4 to 8 mg/L, since concentrations above 9 mg/L appear to be associated with increased adverse events in the elderly (127).

Because of suggestions that valproic acid may be better tolerated than carbamazepine, this agent has recently been suggested as a potential treatment for BDD. To date, however, there are only 4 case series that describe the use of valproic acid for the treatment of agitation in elderly patients (63,172–174). Of 31 patients with dementia and agitation, 9 improved significantly, and 8 others had slight or temporary improvement. Adverse events leading to discontinuation in a small number of patients included sedation, ataxia, and falls. Dosages of valproic acid ranged from 500 to 2500 mg/day, with suggested serum levels of approximately 50 mg/L.

**Buspirone**

Buspirone, a partial 5-HT1A receptor agonist, was first reported as being beneficial for the management of BDD in a case report in 1988 (175). Since then, 3 open-label trials comprising 38 patients, as well as 2 double-blind controlled trials, have been published. In 2 open trials with 26 patients, 38% were rated as significantly improved at dosages of 20 to 45 mg/day (176,177). In the third open-label, dose-finding study (12 patients), there was significant improvement in overall symptoms, as well as a reduction in delusions, aggression, and anxiety at an optimal dose of 30 mg/day (178). In these studies, buspirone was extremely well tolerated, producing only such mild adverse effects as sedation and nausea.

In the first of 2 double-blind, controlled trials, buspirone was compared with trazodone and placebo in 10 patients with dementia (147). There was no change on any behavioural measure compared with placebo, though all patients tolerated the 30 mg/day dose of buspirone well. Besides suffering from the problems inherent in a crossover design, this study also had a small sample size, which may have led to insufficient power and the possibility of a type II error. A recent double-blind trial comparing buspirone 15 mg/day and haloperidol 1.5 mg/day for the treatment of agitation in AD patients contrasts these results. In this 26-patient study, both groups improved significantly over the 10 weeks, though the group receiving buspirone demonstrated greater decreases in anxiety and tension compared with haloperidol (179). In summary, while there is evidence to suggest that buspirone is extremely well tolerated and modestly effective for the treatment of BDD, there are insufficient controlled trials to be able to recommend it for use as a first-line agent.

**Cognitive Enhancers**

There has been a tremendous amount of research into cognitive enhancers over the past decade, but there are still few data to support their efficacy in the treatment of BDD. For example, in 3 large, placebo-controlled trials (180–182), no improvement was noted on the noncognitive subscale of the Alzheimer’s Disease Assessment Scale (183). These negative results, however, may have been a result of only mild baseline behavioural disturbances, which could lessen a potential drug effect, as well as problems associated with the scale itself, which is likely to be more sensitive to cognitive rather than noncognitive changes (184). In contrast to these studies, a recent open-label trial of tacrine suggested that behavioural disturbances were significantly reduced (185). While such uncontrolled studies must be interpreted cautiously, the fact that the study demonstrated a dose–response relationship, as well as a preferential response in the moderately cognitively impaired compared with the severely impaired patients suggests a smaller likelihood that the results are attributable to a placebo effect. In a small, double-blind, crossover study of 2 patients with AD, physostigmine, another acetylcholinesterase inhibitor, was assessed for its effect on BDD (186). Physostigmine decreased hallucinations, agitation, and delusions to a greater degree than haloperidol and had fewer side effects. For the future, studies with newer cognition-enhancing agents should consider subjects with...
significant behavioural disturbances and should use well-validated instruments to measure behavioural change, in addition to cognitive measures.

**Ondansetron**

Ondansetron is a selective 5-HT3 receptor antagonist marketed as an antiemetic for cancer patients receiving chemotherapy. This agent has recently been used in 2 open-label trials of cognitively impaired Parkinson’s disease patients treated with levodopa (187,188). In one study with 7 subjects, visual hallucinations disappeared in 3 patients and decreased in 4 (187). In the second larger trial with 16 subjects, hallucinations completely or almost completely disappeared in 14 patients, improved in one, and were unchanged in one (188). Paranoid delusions were also reduced significantly. Ondansetron was well tolerated in doses of 12 to 24 mg/day, with cognitive and extrapyramidal symptoms unchanged by the treatment.

**Hormonal Therapy**

Treatment of BDD with hormonal manipulation has been documented in several small case reports. These have included the treatment of 4 dementia patients with medroxyprogesterone (189), one patient with conjugated estrogens and a second with diethylstilbestrol (190), one suspected Pick’s disease patient with cyproterone (191), and one Huntington’s disease patient with leuprolide acetate (192). While these studies suggest that these medications were effective and well tolerated, there are concerns about potential adverse effects, which include impotence, hypertension, fatigue, increased appetite, weight gain, edema, loss of body hair, hot flashes, and phlebitis (193). In view of the lack of anecdotal data or controlled trials, there is little support recommending the use of these agents at present.

**Conclusion**

There are several popular treatment algorithms for the pharmacological management of BDD (10,83,124). For example, Yudofsky and others (124) recommend the use of neuroleptics for aggression with psychosis, carbamazepine for aggression with seizures, lithium for aggression with mood symptoms, and buspirone for aggression with anxiety. While such recommendations may appear “rational,” there are insufficient data based on the studies reviewed previously to support the use of such algorithms. Currently, evidence-based practice would suggest the use of neuroleptics as first-line therapy for the treatment of BDD based on the relatively large number of positive controlled trials with these drugs. Should treatment with neuroleptics be unsuccessful, not tolerated, or contraindicated, there is increasing support for the use of antidepressants (for example, SSRIs or trazodone) or carbamazepine. The use of β-blockers, benzodiazepines, buspirone, lithium, valproic acid, cognitive enhancers, or hormonal therapies still requires far more support from controlled trials in order to determine the place of these agents in the management of behavioural disturbances. Ultimately, trials designed to test algorithms, such as the one described previously, will be extremely helpful because there is increasing evidence to suggest that various types of disturbances have different underlying etiopathology and might therefore respond to different agents. This type of behaviour-specific targeted approach may eventually be complemented by a transmitter-specific approach based on the emerging data on neurochemistry reviewed previously. Only then will treatment be truly “rational.”

### Clinical Implications

- Dysfunction in multiple neurotransmitter systems has been found in BDD.
- Neuroleptics are the best-studied group of medications to treat BDD, and modest efficacy has been demonstrated.
- Other promising pharmacotherapies for BDD include antidepressants (for example, trazodone and SSRIs) and anticonvulsants (for example, carbamazepine).

### Limitation

- More studies of the pharmacotherapy of BDD using placebo-controlled parallel designs are urgently needed.

**Acknowledgement**

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**References**


Résumé

Toile de fond : Les troubles du comportement liés à la démence sont une cause fréquente de morbidité excessive, ce qui compromet la qualité de vie du patient et du dispensateur de soins. Dans le cadre d’une approche exhaustive du traitement, qui comprend une recherche des causes sous-jacentes et des interventions comportementales, la pharmacothérapie peut être extrêmement utile pour soulager des symptômes, comme l’agitation, l’agression et la psychose.

Méthode : Dans cet article, on examine de récentes études portant sur le fondement neurochimique de ces troubles du comportement pour justifier le recours à diverses classes de psychotropes.

Résultats : Bien que les neuroleptiques constituent la classe de médicaments jusqu’ici la mieux étudiée, leur efficacité moyenne et leurs effets secondaires potentiels importants en limitent souvent l’utilisation. De nouveaux neuroleptiques atypiques pourraient être mieux tolérés, même si des données contrôlées restent à publier. De plus en plus, on favorise le recours à la carbamazépine et aux antidépresseurs, comme le trazodone et les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS).

Conclusion : D’autres études contrôlées de tous ces agents sont nécessaires pour déterminer si des interventions visant un transmetteur ou un comportement spécifique justifient véritablement une pharmacothérapie efficace contre ces troubles.