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Alternatives to Atypical Antipsychotics for the Management of Dementia-Related Agitation

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Abstract

Numerous recent studies have challenged the widely held belief that atypical antipsychotics are safe and effective options for the treatment of behavioural problems such as agitation in patients with dementia. Accordingly, there is a need to reconsider the place of atypical antipsychotics in the treatment of patients with dementia. The present article is intended to assist clinicians with the assessment and pharmacological management of agitation in patients with dementia. We review the risk-benefit evidence for the use of atypical antipsychotics in patients with dementia-related agitation (DRA). Emerging evidence indicates that, for

patients with dementia, the risks associated with atypical antipsychotics may outweigh the benefits except for patients with severe agitation who require short-term chemical restraint. We then discuss the importance of a careful assessment to rule out potentially reversible factors contributing to DRA. Finally, we summarize the evidence supporting the use of medications other than antipsychotics to treat DRA. There is wide variability in the levels of evidence supporting the use of non-antipsychotic medication for the treatment of DRA. The best evidence currently exists for cholinesterase inhibitors and serotonin-specific reuptake inhibitor antidepressants. Emerging reports suggest that numerous other medications, for example, antiepileptics, lithium, anxiolytics, analgesics, β-adrenoceptor antagonists, cannabinoid receptor agonists and hormonal agents, may prove to be viable alternatives to antipsychotics for the treatment of severe DRA and more research is urgently needed to help assess the effectiveness of these agents. A comprehensive biopsychosocial assessment and treatment plan is likely the most effective way to manage DRA.

Recent studies have yielded data that challenge the safety and efficacy of atypical antipsychotics for the treatment of dementia-related agitation (DRA). Consequently, the US FDA and other regulatory bodies have posted warnings against the use of atypical antipsychotics for the treatment of dementia-related behavioural disorders.[1-3] The present article is intended to assist clinicians with the assessment and management of agitation in patients with dementia. We review the risk-benefit evidence for atypical antipsychotics in patients with DRA. We then discuss the importance of careful assessment to rule out potentially reversible factors contributing to DRA. Finally, we summarize the evidence supporting the use of medications other than antipsychotics to treat DRA.

1. Risks Associated with Atypical Antipsychotics in Patients with Dementia

1.1 Presence of Harm

In 2002, an advisory letter jointly published by Health Canada and the manufacturer of risperidone alerted clinicians to potentially serious risks associated with use of this medication in patients with dementia.[4] The warning was based on the results of a pooled analysis of four placebo-controlled trials showing that strokes were twice as common in patients with Alzheimer-type or vascular dementia receiving risperidone (4%) than in those receiving placebo (2%). In 2004, the FDA followed with a similar advisory on risperidone.[5] Evidence of analogous problems has also emerged for olanzapine.[6,7] Indeed, numerous studies suggest that atypical antipsychotics in general may be associated with an increased risk of stroke and/or death in patients with dementia.[8-14] Shortly thereafter in 2005, the FDA released a public health advisory that warned of increased mortality in patients with dementia treated with atypical antipsychotics.[1-3] This advisory was based on the results of a 2005 meta-analysis (17 placebo-controlled trials, 5106 patients, 10-week average duration) that found increased mortality (4.5% with the use of olanzapine, aripiprazole, risperidone and quetiapine vs 2.6% with placebo) in patients with DRA. The FDA extrapolated a class effect based on the finding of increased mortality with atypical antipsychotics from all three classes of chemical structure. Accordingly, the warning extends to use of the atypical antipsychotics clozapine and ziprasidone despite the fact that their effect on mortality has not been adequately studied in patients with dementia. In 2006, the authors of a Cochrane review concluded that although risperidone and olanzapine may reduce aggression in dementia, and although risperidone may reduce dementia-related psychosis, both medications are associated with a significant risk of serious adverse effects or death.[15] The authors conceded that there may be a limited role for the short-term use of these medications in patients with dementia who develop severely distressing, dangerous symptoms.[15,16]

In addition to the apparently increased risk of stroke or death, antipsychotics have other common adverse effects that must also be considered. Atypical antipsychotics, particularly olanzapine, have anticholinergic properties that can increase the risk of confusion, agitation and delirium in a dose-dependent manner.[17] Furthermore, the risk of extrapyramidal adverse effects, particularly with risperidone, is significant, especially in patients with Lewy body/Parkinson's dementia[18] and patients with frontotemporal dementia.[19]

1.2 Absence of Harm (Unclear Evidence/ Mechanism)

There is some evidence, albeit from studies of lower quality, that challenges the notion that use of atypical antipsychotics in patients with dementia increases the risk of stroke and/or death. After controlling for age, medical co-morbidity and dementia symptom severity, the authors of a prospective study including 273 patients found no increase in the 1-year mortality rate of patients receiving antipsychotics.[20] A large 18-month case-control study of elderly nursing home residents (1130 patients and 3658 control subjects) found no increased risk of cerebrovascular events associated with antipsychotic use although the sample was not limited to patients with a diagnosis of dementia. Data from this study suggest that pre-existing cerebrovascular risk factors may increase the risk of cerebrovascular events in patients receiving olanzapine, clozapine or quetiapine, but not in patients receiving risperidone or conventional antipsychotics.[21] A 3-year retrospective cohort analysis of Medicaid data from almost 19 000 patients with dementia found a reduced incidence of hospital admissions for cerebrovascular events in patients starting antipsychotic treatment compared with benzodiazepine treatment (odds ratio = 0.49, $p < 0.05$) within 3 months of medication initiation.[22] A 12-month open-label study comparing olanzapine use (mean dose 4.23 mg/day) in 173 patients with vascular dementia and behavioural problems with conventional antipsychotic use in 173 similar patients showed improvement in both groups without any observed cerebrovascular events.[23] An acute treatment study of 39 extended-care patients with dementia and behavioural disturbances found that both risperidone (mean dose 1.47 mg/day) and olanzapine (mean dose 6.65 mg/day) titrated to effect over 2 weeks were equally effective and well tolerated.[24] The findings from these latter two studies appear to support use of low-dose, short-term antipsychotics for the treatment of DRA.

For obvious ethical reasons, it is difficult, if not impossible, to conduct prospective controlled studies seeking to clarify the nature and risk of potential harms associated with treatments. This is especially problematic in studies of patients with dementia, who are often incapable of consenting to participation in research. The reports we reviewed were mainly limited to retrospective cohort and case-control studies as well as relatively brief, open-label prospective studies. Overall, the 'absence of harm' evidence base appears less robust than the 'presence of harm' evidence base. Given the apparent absence of a putative mechanism to account for the association between atypical antipsychotics and stroke, some investigators called for more specific research to help clarify the nature of the risk as well as the mechanism(s) responsible.[25,26] The authors of one recent systematic review exposed significant gaps in the evidence base by highlighting the number of randomized controlled trials with heterogeneous and/or incomplete harms reporting.[27]

1.3 Comparisons with Conventional Antipsychotics

Disappointed with the safety profile of atypical antipsychotics, some clinicians have contemplated reverting back to the use of older, first-generation antipsychotic medications to help control agitation in their patients with dementia. Indeed, there is some evidence that in patients with dementia, atypical antipsychotics such as risperidone are associated with a higher risk of stroke than conventional antipsychotics such as haloperidol.[28] Conventional antipsychotics may approximate the effect of atypical antipsychotics, but with a higher risk of neurological adverse effects.[11,29,30] The risk-benefit profile of conventional antipsychotics appears consistent across the entire class,[31] although thioridazine has specific risks (e.g. dizziness, anticholinergic effects, prolonged corrected QT interval) that outweigh any potential benefits for patients with dementia.[32] A recent double-blind comparison of olanzapine and

haloperidol found no difference in tolerability or efficacy[33] but a double-blind crossover comparison found that risperidone was both more efficacious and better tolerated than haloperidol for the treatment of agitation in patients with dementia.[34] A large retrospective cohort study did not find a significantly higher risk of stroke with risperidone or olanzapine compared with conventional antipsychotics.[35] On the other hand, there is evidence suggesting an increased risk of mortality[36] and stroke[37] with both conventional and atypical antipsychotics when used in patients with dementia. The authors of a retrospective cohort study of >37 000 patients aged ≥65 years (but not necessarily diagnosed with dementia) interpreted their data to suggest that the mortality risk associated with conventional antipsychotic use approximates and possibly exceeds the mortality risk associated with use of atypical antipsychotics.[38] The authors of another retrospective cohort study of >22 000 patients with dementia concluded that conventional antipsychotic medications were associated with a significantly higher risk of death than atypical antipsychotics throughout the treatment period.[39] Accordingly, the FDA's 2005 public health advisory also includes a precautionary statement on the use of conventional antipsychotics in patients with dementia.[1]

Both atypical and conventional antipsychotics have been associated with significant risks in elderly patients as well as in patients with dementia. It is important to remember that, in addition to the potential mortality and morbidity risks (e.g. cerebrovascular and neurological adverse events), antipsychotics have numerous other adverse effects, including anticholinergic, metabolic and cardiovascular (e.g. hypotension, cardiac conduction abnormalities) effects. By taking into account the specific risk-benefit considerations in patients with dementia, clinicians can determine when an antipsychotic is necessary and select one to match the needs of an individual patient, administered on a short-term basis at the lowest effective dose.

2. Effectiveness of Atypical Antipsychotics in Patients with Dementia

2.1 Does the Potential Effectiveness of Atypical Antipsychotics Outweigh the Potential Risks?

In addition to the growing evidence highlighting the risks of atypical antipsychotics in patients with dementia, there is new evidence that the effectiveness of atypical antipsychotics may not outweigh the potential risks. The CATIE-AD (Clinical Antipsychotics Trial of Intervention Effectiveness in Alzheimer's Disease) was a US government-funded, randomized, controlled, multicentre trial of risperidone (mean dose 1 mg/day), olanzapine (mean dose 5.5 mg/day) and quetiapine (mean dose 56.5 mg/day) for the treatment of psychosis, aggression or agitation in 421 outpatients with Alzheimer's disease.[40] In an attempt to assess treatment effectiveness in a naturalistic setting, the study measured differences in time to treatment discontinuation because of lack of effectiveness, intolerability or for any reason. The study also measured differences in improvement on the Clinical Global Impression of Change (CGI-C) scale. The investigators reported no significant difference in the median time to discontinuation of treatment for any reason in patients taking risperidone (7.4 weeks), olanzapine (8.1 weeks), quetiapine (5.3 weeks) or placebo (8 weeks). Although the median time to discontinuation of treatment due to lack of effectiveness was significantly longer for olanzapine (22.1 weeks; mean final dose 5.5 mg/day) and risperidone (22.7 weeks; 1 mg/day) compared with quetiapine (9.1 weeks; 56.5 mg/day) and placebo (9 weeks) [$p = 0.002$], any positive effect of the former two agents appeared to have been negated by harmful outcomes as the time to discontinuation due to adverse events or intolerability favoured placebo ($p = 0.009$). Differences in CGI-C response rates favoured olanzapine over placebo (32% vs 21%, respectively; $p < 0.05$), but the differences observed with risperidone (26%) and quetiapine (29%) were not significant. Although a full critical review of this landmark study is beyond the scope of our discussion, it is important to note that the CATIE-AD subjects were outpatients and the results therefore may not neces-

sarily be generalizable to patients with more severe DRA who require hospitalization. Another recent trial found no significant difference between risperidone or olanzapine versus placebo in the treatment of psychosis and associated behavioural disturbances in patients with dementia although improvement was noted in all groups.[41] Yet another study found no significant difference between quetiapine or rivastigmine versus placebo for the treatment of DRA.[42] These findings raise the possibility that DRA may improve somewhat simply as a result of the attention and structure inherent in study participation (the Hawthorne effect). A systematic review of this topic revealed no difference between atypical antipsychotics and placebo in two of the five trials reviewed.[43]

Although this evidence raises additional concern regarding widespread use of atypical antipsychotics in outpatients with dementia, it should be considered in the context of a robust evidence base suggesting that these medications can effectively treat DRA. Four systematic reviews and a pooled analysis have found evidence that atypical antipsychotics are more effective than placebo.[11,44-47] This conclusion is supported by a large number of studies yielding various levels of evidence that risperidone[34,48-68] and olanzapine[24,68-72] appear to be effective treatments. Quetiapine may also be an effective treatment, although the level of evidence for this agent is not as robust.[68,73-76] One retrospective study found global improvement in patients with dementia who were switched from risperidone to quetiapine.[77] A recent placebo-controlled trial showed that quetiapine 200 mg/day reduced agitation whereas a regimen of 100 mg/day did not.[78] This contrasts with previously disappointing results for quetiapine at lower doses, such as in the CATIE-AD (mean daily dose 56.5 mg) trial[40] and in the comparison trial with rivastigmine versus placebo (daily dose 50–100 mg).[42] It may therefore be necessary to increase the daily dose of quetiapine to 200 mg or more, as tolerated. In a recent randomized, placebo-controlled trial, 10 mg/day of aripiprazole, a novel atypical antipsychotic with properties including partial agonism at dopamine D_2 receptors, partial agonism at serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors, was efficacious and safe in patients with dementia, improving psychotic symptoms, agitation and clinical global impression.[79] Benefits for aripiprazole in the treatment of DRA have also been described in other reports.[80,81] There are isolated reports of other atypical antipsychotics effectively treating DRA, including clozapine,[82] amisulpride,[83] ziprasidone,[84] zotepine[85] and tiapride.[86] Agitated patients with Lewy body/Parkinson's dementia may also benefit from treatment with olanzapine[87] or quetiapine.[88]

Clinicians may therefore take solace in the fact that a substantial evidence base supports the use of atypical antipsychotics, particularly risperidone and olanzapine, for the treatment of DRA. Taking into account the recent results of CATIE-AD,[40] as well as the emerging evidence of stroke and mortality risk, clinicians should limit use of atypical antipsychotics to short-term treatment of severe agitation in patients with dementia. Given that this population represents a relatively small proportion of patients with dementia, clinicians will need to consider other options for the routine assessment and management of DRA. In section 3, we review some practical approaches to assessment of DRA and summarize the evidence for different management options.

3. Practical Approaches to the Assessment and Management of Dementia-Related Agitation

3.1 Ensure the Safety of the Patient and People Nearby

In an acute behavioural crisis, protection of the patient and of people nearby is of paramount importance. In preparation for such events, staff routinely working with patients with dementia should receive up-to-date behavioural crisis intervention training. Caregivers faced with an acute behavioural crisis should notify community emergency services or hospital support staff for urgent back-up. Temporary application of the least chemical and/or physical restraint necessary to protect the patient and people nearby may be required.

3.2 Describe and Document the Agitation

A common and practical method of identifying and tracking DRA is the so-called 'ABC' method. This involves careful documentation of the **A**nte-

cedent(s) or potential trigger(s) of the behaviour, the **B**ehavioural description and the **C**onsequence review, that is, what happens after the agitation emerges. To help identify behavioural patterns, it may be useful to describe the general type of DRA (e.g. verbal, physical, sexual) and for each type, establish if it appears spontaneously or in response to an environmental stimulus.

3.3 Check the Behavioural Vital Signs

Prescribing pharmacological or non-pharmacological interventions for behavioural disturbances in dementia requires systematic measurements of target symptom clusters, including their frequency, severity and impact. For this purpose, we suggest a simple, user-friendly one page observational chart called 'The Behavioural Vital Signs (BVS) tool'.[89] This may be downloaded free of charge from the Canadian Academy of Geriatric Psychiatry website (http://www.cagp.ca/en/newsletters/e_newsletter1/bvs_tool.pdf). Use of the BVS tool facilitates much more detailed identification and tracking of target symptom clusters, allowing clinicians to identify behavioural patterns and analyse and correct specific factors associated with the agitation. The BVS tool also allows for quantification of symptom severity and can be used to track the effectiveness of an intervention.

3.4 Rule Out Potentially Reversible Factors

Many cases of DRA can be treated simply by identifying and removing causative factors. This is a critical step and should not be overlooked. Patients with dementia are often not able to provide a reliable history or even a meaningful description of discomfort. Furthermore, such patients are often uncooperative, resistive or even aggressive in response to attempts at physical examination. Accordingly, because clinicians must hunt carefully for potentially reversible problems, often without help from the patient, it is all too tempting to gloss over this assessment, conclude that the agitation is 'dementia-based' or 'BPSD' (behavioural and psychological symptoms of dementia) and prescribe a medication. Close collaboration with hands-on caregivers is essential since clues often emerge from physical inspection and/or manipulation of the patient during personal care (e.g. a patient wincing or grimacing can be suggestive of pain or tenderness).

As is well known for delirium, potentially reversible causes of DRA are usually multi-factorial. To help guide clinicians through this process, we divide these factors into two groups: biological (table I) and psychosocial (table II). Biological factors are subdivided into endogenous and exogenous factors. Endogenous biological factors can usually be ruled out by a careful review of systems and physical examination, using collateral history and other clues to fill in any gaps arising from poor patient reliability and/or cooperation. Screening laboratory investigations are also justified when clinicians have a high index of suspicion for a specific problem.

Table III and figure 1 show other useful strategies for the management of DRA including the 'S.M.A.R.T' mnemonic[90] and a five-step clinical algorithm adapted from Mintzer and Brawman-Mintzer.[91]

4. Pharmacological Alternatives for Dementia-Related Agitation

Despite careful assessment to rule out potentially reversible contributing factors and assiduous, creative application of non-pharmacological management strategies, clinicians still require pharmacological options for the amelioration of DRA. Indeed, medication use can be a key component of a comprehensive biopsychosocial approach to the management of DRA. Although antipsychotics still have a role in the short-term treatment of severe DRA, other pharmacological agents merit consideration in the short- and long-term management of DRA. However, we must emphasize that the evidence base supporting the use of these different medications is highly variable and often limited to anecdotal reports or case reviews. The current evidence base supporting various non-antipsychotic medication options for the treatment of DRA is discussed in sections 4.1–4.9 and a summary (including common drug doses) is presented in table IV.

4.1 Cholinesterase Inhibitors and Nicotinic Receptor Agonists

Like antipsychotic medications, cholinesterase inhibitors play an important role in the short-term,

Table I. Dementia-related agitation: potentially reversible biological factors

Endogenous	Exogenous
Pain/discomfort	Medications
musculoskeletal pain	prescription (corticosteroids, salbutamol [albuterol],
headache	amphetamines, antidepressants, benzodiazepines,
tooth/jaw/throat/neck pain	anticholinergics, opioids, antiepileptics,
eye/ear/nose/sinus pain	cholinesterase inhibitors, memantine)
chest pain	toxicity (lithium, phenytoin, digoxin)
gastrointestinal pain (GERD, *Helicobacter pylori* [especially if anorexic], constipation)	over-the-counter drugs (pseudoephedrine, dextromethorphan, diphenhydramine, dimenhydrinate)
genitourinary pain (dysuria/UTI, prostatism/retention)	herbal (ginseng, guarana, hypericum [St John's wort])
dermatological pain (rash, allodynia/neuropathic [e.g. post-herpetic neuralgia])	Substance abuse/withdrawal
neurological pain (headache, spinal stenosis/impingement, neuropathic [e.g. DM, PHN])	alcohol
foot pain (onychomychosis, DM, oedema/venous stasis/ dermatitis)	caffeine
Infectious	nicotine
respiratory tract infection	other (including cocaine, amphetamine, cannabis)
viral gastroenteritis/*H. pylori*/*Clostridium difficile*	Diet
UTI	intolerance (lactose, gluten [celiac disease])
cellulitis	caffeine
Metabolic	sugar
thyroid disease	Toxins
adrenal disease	
uncontrolled DM	
hypoxia	
anaemia	
Neuropsychiatric	
depression (psychomotor agitation, retardation or both)	
anxiety	
mania	
psychosis	
atypical seizure disorder (temporal/frontal lobe seizures)	

DM = diabetes mellitus; **GERD** = gastro-oesophageal reflux disease; **PHN** = post-herpetic neuralgia; **UTI** = urinary tract infection.

symptomatic treatment of DRA. Numerous recent reviews yield evidence confirming the general clinical impression that cholinesterase inhibitors improve behavioural disturbances in dementia.[92-94] A recent *post hoc* pooled analysis of three placebo-controlled galantamine trials in patients with mild-to-moderate Alzheimer's disease showed significant improvements in behavioural symptoms.[95] The findings suggest that a specific group of symptoms, including hallucinations, anxiety, apathy and aberrant motor behaviour, may respond to enhancement of cholinergic transmission. Rivastigmine use has been correlated with behavioural improvements in patients with moderate-to-severe Alzheimer's disease.[96] Furthermore, a recent systematic review found that rivastigmine use was correlated with improvement in behavioural symptoms across a wide variety of dementia subtypes.[97] Donepezil use is also widely associated with improvements in DRA, mood and delusional symptoms;[98-101] however, a recent 12-week randomized, placebo-controlled trial of donepezil failed to show a significant reduction in agitation.[102] Similarly, rivastigmine did not significantly reduce DRA in a placebo-controlled trial of up to 26 weeks' duration.[42] These results suggest that cholinesterase inhibitor-mediated improvements in DRA may evolve gradually, after the first 3–6 months of treatment.

To help account for some of this conflicting evidence, some authors have suggested that although behavioural symptoms often improve in patients with cholinesterase inhibitor-induced enhancement of frontal cholinergic neurotransmission, many studies fail to identify such improvements because of methodological issues such as use of instruments not designed for measuring these

Table II. Dementia-related agitation: potentially reversible psychosocial factors

Communication breakdown
Perceptual problems
Visual: appropriate ambient/background lighting, appropriate corrective lenses, approach from front, may need to accentuate non-verbal signals (facial expressions, body language, hand gestures), consider possible illusions or hallucinations, consider possible misidentification
Hearing: appropriate ambient/background noise, loud and clear speech with low tone, ensure no cerumen plug in external meatus, appropriate hearing aid/amplification device, consider possible illusions or hallucinations
Language barrier
Ensure translater present if necessary
Environmental factors
Excessive stimulation
Social: excessive social pressure, e.g. numerous visitors, simultaneous conversations
Audiovisual: excessive noise/light, e.g. loud television/radio/staff/co-patients
Inadequate stimulation
Social: isolation/loneliness/boredom
Temperature
Patient area too hot/cold
Functionality
Inappropriate clothing: size, material, shoes
Inappropriate furniture: bed/mattress/chairs/tables/bathroom
Inappropriate medical equipment: wheelchair/walker/cane
Dietary preference/requirements
Transfers to and from home/facility/hospital
Family factors
Family conflict
Family caregiver strain
Estate administration issues
Financial concerns
Absence/loss of family supports

changes with sufficient sensitivity.[103] Insufficient trial duration might also account for the lack of improvement in DRA observed by the 12- and 26-week mark in the placebo-controlled trials cited earlier. Other specific problems such as inappropriate sexual behaviour may decrease with cholinesterase inhibitor therapy.[104] Direct stimulation of nicotinic cholinergic receptors with transdermal nicotine has been used to treat DRA.[105] In patients with Lewy body/Parkinson's dementia, cholinesterase inhibitors are known to improve a variety of neuropsychiatric symptoms, including agitation and psychosis.[106-109]

The balance of evidence and clinical experience suggests that cholinesterase inhibitor use is associated with an improvement in DRA with better tolerability than antipsychotic agents. However, some authors would argue that even if statistically significant behavioural effects are emerging in the literature, the efficacy evidence for use of cholinesterase inhibitors remains weak and the clinical significance of these effects is not robust. Furthermore, behavioural improvements are typically seen only after weeks to months of cholinesterase inhibitor treatment. Treatment with cholinesterase inhibitors also might delay or obviate the need to eventually use antipsychotic agents.[110] Perhaps more widespread use of cholinesterase inhibitors in mild, moderate and severe dementia, targeting cognitive/functional symptoms as well as neuropsychiatric symptoms such as DRA, would further limit the role of antipsychotic agents to the very short-term treatment of severe, dangerous agitation.

4.2 Memantine

Memantine, an NMDA-glutamate receptor antagonist recently approved for the treatment of moderate-to-severe Alzheimer's disease, is associated with a reduced rate of symptom progression as well as improvement in function and DRA.[111-113] Some reports suggest that use of memantine can lead to a clinically significant improvement in DRA.[114] However, a recent Cochrane review[115] questioned the clinical significance of statistically significant results favouring memantine. The average improve-

Table III. The 'S.M.A.R.T' approach to management of dementia-related agitation[90]

Safety	Ensure safety of patient, staff and other residents
Medical	Work-up to treat reversible causes; reduce toxic medication load
Assess competency	Address issues relating to consent for personal care decisions, financial matters, driving; protect assets
Rest	Review other causes of agitation, e.g. eyes, ears, teeth, mouth, bowels, bladder, skin, feet, nutrition, hydration, pain, ambulation, environmental temperature, noise level, etc.
Trial of medication	Pharmacological risk-benefit assessment. Involve a substitute decision-maker if the patient is incapable of providing informed consent

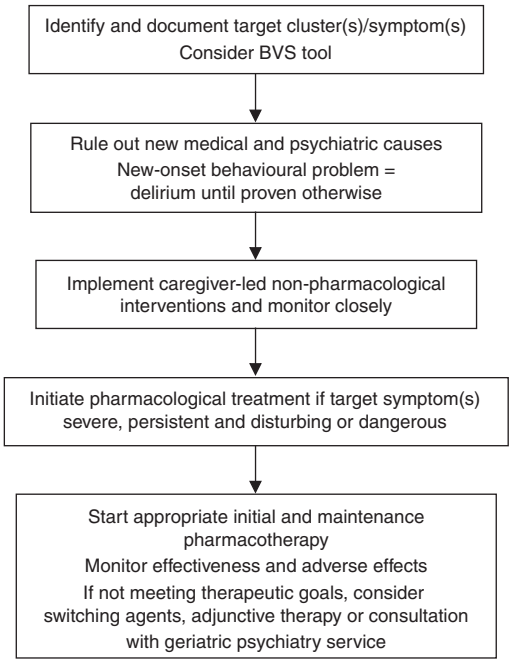

Fig. 1. Algorithm for management of dementia-related agitation (adapted from Mintzer and Brawman-Mintzer[91]). **BVS** = Behavioural Vital Signs.[89]

ment of 2.8 points on the 144-point Neuropsychiatric Inventory may be undetectable by clinicians and caregivers. Another study suggested that memantine spares antipsychotic use for the treatment of DRA.[116] On the other hand, memantine has been associated with a worsening of symptoms such as agitation and hallucinations,[117] particularly in patients with Lewy body dementia.[118,119]

4.3 Antidepressants

Antidepressants may improve not only dementia-related depression but also behavioural symptoms such as DRA. Indeed, major depressive disorder is common in elderly patients and may represent a contributory if not the primary cause of agitation in patients with dementia. The antidepressants with the best evidence for efficacy in the treatment of DRA are the selective serotonin reuptake inhibitors (SSRIs). It has been postulated that DRA is related to central serotonin deficits[120] and frontal lobe dysfunction,[121] making frontal serotonin systems a logical target for the treatment of behavioural symptoms.[98] Enhanced frontal serotonin neurotransmission may also help stabilize cognition.[122]

In a number of reports, citalopram use has been associated with a reduction in several behavioural symptoms, including DRA.[123-125] A recent 12-week double-blind trial showed similar rates of improvement in DRA and psychosis in patients treated with citalopram versus risperidone, with significantly more adverse effects reported in the risperidone group.[126] Another recent trial showed that citalopram improved DRA to a more significant degree than perphenazine, compared with placebo.[127] The second phase of CATIE-AD will assess the effectiveness of citalopram in patients who did not improve with or who could not tolerate atypical antipsychotics.[40] Sertraline has also been shown to improve DRA. Factors associated with a favourable response to sertraline include female gender and low aggression.[128] The third phase of a recent donepezil study will assess the effect of sertraline on dementia-related neuropsychiatric symptoms.[98] Trazodone is a mixed serotonin reuptake inhibitor and post-synaptic serotonin ($5\text{-}HT_{2A}$)-receptor blocking antidepressant with sedating properties due to histamine receptor blockade. A few reports suggest that trazodone can be an effective and well tolerated treatment for DRA,[129-131] although a recent Cochrane review was inconclusive, with the authors calling for more research.[132] A trial comparing trazodone with haloperidol for the treatment of DRA found that although both medications improved DRA, trazodone was better tolerated.[131] On the other hand, a noteworthy finding in another trial was the comparable effectiveness of trazodone, haloperidol and caregiver training for the treatment of DRA.[133] Agitation in patients with dementia who have a co-morbid mood disorder can also be treated with electroconvulsive therapy.[134-137]

In summary, there is an expanding literature base supporting the use of serotonin reuptake inhibitor antidepressants for the treatment of DRA. Among antidepressants, the best evidence exists for citalopram, sertraline and trazodone, although the efficacy evidence remains weak overall.

4.4 Antiepileptics

Selected antiepileptics are commonly used to treat mood disorders and behavioural problems in

Table IV. Pharmacological alternatives to antipsychotics for the treatment of dementia-related agitation

Medications	Applications/comments
Cholinesterase inhibitors	
Galantamine (8–24 mg/day)	Evaluated in multiple randomized controlled trials
Donepezil (5–10 mg/day)	Can improve agitation, mood, anxiety, apathy and psychotic symptoms
Rivastigmine (3–9 mg/day)	Especially effective in patients with Lewy body dementia
	Gastrointestinal adverse effects can limit tolerability
NMDA-glutamate receptor antagonist	
Memantine (10–20 mg/day)	Evaluated in multiple randomized controlled trials
	Small-to-moderate effect size
	Can stabilize cognition, function and agitation
	Possible antipsychotic-sparing effect
	May worsen agitation or psychotic symptoms in some patients
Antidepressants	
Citalopram (10–40 mg/day)	Evaluated in multiple randomized controlled trials
Sertraline (25–200 mg/day)	SSRIs are the most effective and best tolerated antidepressants
Trazodone (12.5–200 mg/day)	Target agitation resulting from co-morbid depressive disorders
	May reduce agitation via enhancement of frontal serotonin neurotransmission
	Monitor for SIADH-related hyponatraemia and movement disorders
Antiepileptics	Fair evidence base
Valproic acid (250–1500 mg/day)	Valproic acid may have a narrow therapeutic dosage window for the treatment of agitation (750–1000 mg/day)
Carbamazepine (100–600 mg/day)	Carbamazepine use may be complicated by numerous adverse effects and hepatic auto-induction
Gabapentin (200–2700 mg/day)	Gabapentin dosage must be reduced in patients with renal impairment
Lithium	Poor evidence base
(150–600 mg/day)	May reduce agitation with prominent affective lability
	Requires frequent monitoring of serum levels (target 0.2–0.6 mmol/L), renal and thyroid function
	Monitor for tremor, ataxia, confusion, toxicity
	May be neuroprotective
Anxiolytics	Poor evidence base
Benzodiazepines	Benzodiazepines can be helpful for short-term treatment of agitation accompanied by severe anxiety
Buspirone	Use when agitation is triggered by alcohol or benzodiazepine withdrawal
	Monitor for ataxia, confusion, disinhibition
Analgesics	Poor evidence base
Paracetamol (acetaminophen [up to 4 g/day])	Use when pain is suspected as a factor contributing to agitation
NSAIDs/COX-2 inhibitors	
Opioids	
SNRIs	
Gabapentin/pregabalin	
β-Adrenoceptor antagonists	Poor evidence base
Propranolol	Avoid in patients with a history of asthma/COPD
Pindolol	Caution in patients with cardiovascular disease
Cannabinoid receptor agonists	Poor evidence base
Nabilone (0.5–1 mg/day)	May improve anorexia and agitation

Continued next page

Table IV. Contd

Medications	Applications/comments
Dronabinol	Possible neuroprotective and disease-modifying properties
	Possible cholinesterase inhibition properties
Hormonal treatments	Poor evidence base
Anti-androgen agents (cyproterone, leuprorelin [leuprolide], estrogen, goserelin)	Anti-androgen agents may reduce sexual disinhibition/aggression in men with agitation
Melatonin (3–9 mg in the evening)	Melatonin may reduce nocturnal agitation/insomnia

COPD = chronic obstructive pulmonary disease; **COX** = cyclo-oxygenase; **SIADH** = syndrome of inappropriate antidiuretic hormone; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

patients with CNS disorders. There is some evidence that antiepileptics may reduce DRA as well. For valproic acid, the information is somewhat conflicting. Many studies have yielded promising results,[138-143] although conclusions drawn from a recent controlled trial[144] and a Cochrane review[145] have been disappointing. It seems that valproic acid may have a narrow therapeutic window for the treatment of DRA, whereby low doses (<800 mg/day) are not effective[144] and high doses (1000–1500 mg/day) are poorly tolerated.[146] Similarly, carbamazepine may be effective for DRA[147-150] but use of this agent is often limited by adverse effects as well as pharmacokinetic drug interactions secondary to its enzyme-inducing effect. Preliminary results suggest that carbamazepine may specifically reduce dementia-related sexual disinhibition[151] as well as DRA that is refractory to treatment with other medications.[152,153] Other antiepileptics with potential effectiveness against DRA include gabapentin[154] and topiramate.[155] Oxcarbazepine may be better tolerated with less hepatic auto-induction than carbamazepine[156] and research is needed to investigate the role of oxcarbazepine in the treatment of DRA.

4.5 Lithium

Lithium can effectively treat behavioural disturbances across a spectrum of neuropsychiatric disorders in patients of all ages.[157,158] In elderly patients, clinicians can optimize the tolerability of lithium by targeting lower serum levels (0.2–0.6 mmol/L) and monitoring closely for adverse effects and chronic toxicity, especially in patients with pre-existing renal dysfunction. Although cognitive adverse effects can complicate lithium use in the elderly, lithium may actually have neuroprotective qualities, the specific benefits of which require investigation in patients with dementia.[159] On the other hand, a recent hypothesis-generating study found a history of lithium use to be associated with a higher rate of dementia.[160] There are reports of lithium use for the treatment of behavioural disturbances in patients with dementia[161,162] but no controlled trials have been published.

4.6 Anxiolytics

Anxiety is often associated with DRA although it is probably not a necessary antecedent.[163] Although elderly patients should generally avoid using benzodiazepines because of the risk of adverse effects and dependence, this class of medication can be effective for the short-term management of severe anxiety that can accompany DRA. Benzodiazepines are indicated when DRA is related to alcohol and/or benzodiazepine withdrawal, which are common factors that are often overlooked in patients with dementia who become agitated shortly after hospitalization. One study found that alprazolam was an acceptable alternative to low-dose haloperidol for the treatment of DRA.[164] If benzodiazepines must be used in patients with dementia, temporary use of agents with a brief half-life (such as lorazepam, oxazepam or temazepam) is preferred. Other than a select few case reports, there is little information on which to assess the atypical anxiolytics, including partial 5-HT_{1A} receptor agonists such as buspirone[165,166] and tandospirone,[167] in the treatment of DRA.

4.7 Analgesics

If there is a high index of suspicion that pain is contributing to DRA but it is difficult to reliably

identify and treat active sources of pain, an empirical trial of analgesic medication may be a reasonable option. Certain rating scales may be useful tools to help assess pain and its relationship to agitation in patients with dementia.[168,169] Regular maximal daily dosages of paracetamol (acetaminophen) [up to 1000 mg every 6 hours] can be attempted as long as baseline liver function is intact. Opioid analgesics are best avoided because of the risk of adverse effects, dependence and tolerance. If chronic pain is clearly contributing to DRA, and if a regular maximum dose of paracetamol does not control the pain, low doses of opioid analgesics may be helpful (e.g. hydromorphone 0.5 mg). When pain is primarily musculoskeletal, judicious use of NSAIDs or cyclooxygenase-2 inhibitors may be indicated. Gabapentin and dual-acting serotonergic and noradrenergic antidepressants can help treat chronic neuropathic pain.[170] Amitriptyline, a standard agent for neuropathic pain, should be avoided in patients with dementia because of the risk of worsening confusion through its anticholinergic action. Assertive physiotherapy is especially important to reduce the risk of pain due to immobility in patients with dementia who are wheelchair-bound or bed-ridden.

4.8 β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists can help reduce situational anxiety, antipsychotic-related restlessness (akathisia) and agitation when administered in high doses to patients who have sustained a traumatic brain injury.[171] In patients with dementia, there are at least two reports of propranolol effectively treating DRA.[172,173] Pindolol may also be an effective treatment for DRA.[174]

4.9 Cannabinoid Receptor Agonists

Cannabinoid receptor agonists are being used to treat nausea, anorexia, pain and anxiety in a number of different conditions.[175-178] CNS cannabinoid receptors may be a novel target for clinicians seeking medication options for the treatment of DRA. Tetrahydrocannabinol may be neuroprotective with potential disease-modifying effects, including acetylcholinesterase inhibition, reduced neuronal excitotoxicity and reduced amyloid aggregation, in Alzheimer's disease.[179-181] In patients with dementia, the cannabinoid receptor agonist dronabinol was found to improve anorexia and DRA[182] as well as nocturnal DRA.[183] One patient with refractory DRA improved significantly while receiving low-dose nabilone (0.5–1 mg/day), another cannabinoid receptor agonist.[184] Increased agitation is listed as a potential adverse effect of these medications, and low doses are therefore initially advisable with a cautious upward dose titration as required.

4.10 Hormonal Agents

Anti-androgen pharmacotherapy is sometimes used to treat sexual disinhibition in male patients with dementia.[185] There is a case report of estrogen use to treat both sexual and general aggression in two male patients with dementia.[186] There is also a recent case report of effective treatment of refractory agitation and aggression in a male patient with goserelin, a gonadotropin-releasing hormone agonist.[187] Melatonin (3–9 mg evening) can improve dementia-related sleep and circadian rhythm disturbances (sundowning).[188-190]

4.11 Summary

There is wide variability in the levels of evidence supporting the use of non-antipsychotic medication for the treatment of DRA. The most robust evidence exists for cholinesterase inhibitors and SSRI antidepressants. Despite this evidence base, practical issues such as slow onset of effect and lack of effect for severe DRA can limit the applicability of these medications in the acute setting. However, in addition to the comprehensive general assessment and management strategies suggested herein, patients with severe DRA may benefit from short-term treatment with an antipsychotic plus long-term treatment with a cholinesterase inhibitor and/or an antidepressant and possibly memantine or a less well established alternative. Emerging reports suggest that certain of the other medications discussed above may prove to be viable alternatives to antipsychotics for the treatment of severe DRA and more research is urgently needed to help assess the effectiveness of these agents.

5. Conclusion

As the global population ages and life expectancy increases, the growing number of people with dementia will likely have profound social and economic consequences. Dementia is a devastating illness and the behavioural symptoms that often emerge can be extremely distressing for patients, family members and caregivers. Assessment and management of DRA can be challenging. A logical approach should entail identification and correction of potentially reversible factors contributing to the agitation. Whenever possible, creative and individualized behavioural and environmental strategies to reduce agitation should be developed and implemented. Medications can be helpful to reduce DRA although the risks of their use must be weighed against the benefits. Emerging evidence indicates that, for patients with dementia, the risks associated with antipsychotic use may outweigh the benefits except for patients with severe agitation who require short-term chemical restraint. Numerous other medication options exist for longer term prevention and treatment of DRA, although the evidence for some remains sparse and controlled trials are urgently needed. Co-morbid major depressive disorder presenting with agitation should be considered and treated with antidepressant medication and/or electroconvulsive therapy. A comprehensive biopsychosocial assessment and treatment plan is likely the most effective way to manage DRA.

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