Original Paper

Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia

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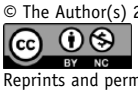
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Abstract

Introduction: Behavioural and psychological symptoms of dementia (BPSD) include agitation and aggression in people with dementia. BPSD is common on inpatient psychogeriatric units and may prevent individuals from living at home or in residential/nursing home settings. Several drugs and non-pharmacological treatments have been shown to be effective in reducing behavioural and psychological symptoms of dementia. Algorithmic treatment may address the challenge of synthesizing this evidence-based knowledge.

Methods: A multidisciplinary team created evidence-based algorithms for the treatment of behavioural and psychological symptoms of dementia. We present drug treatment algorithms for agitation and aggression associated with Alzheimer's and mixed Alzheimer's/vascular dementia. Drugs were appraised by psychiatrists based on strength of evidence of efficacy, time to onset of clinical effect, tolerability, ease of use, and efficacy for indications other than behavioural and psychological symptoms of dementia.

Results: After baseline assessment and discontinuation of potentially exacerbating medications, sequential trials are recommended with risperidone, aripiprazole or quetiapine, carbamazepine, citalopram, gabapentin, and prazosin. Titration schedules are proposed, with adjustments for frailty. Additional guidance is given on use of electroconvulsive therapy, optimization of existing cholinesterase inhibitors/memantine, and use of *pro re nata* medications.

Conclusion: This algorithm-based approach for drug treatment of agitation/aggression in Alzheimer's/mixed dementia has been implemented in several Canadian Hospital Inpatient Units. Impact should be assessed in future research.

Keywords

Dementia, agitation, drug treatment, algorithm

Introduction

Over 35 m people have dementia worldwide (Prince et al., 2013) and the prevalence is anticipated to double every 20 years (Ferri et al., 2005). Alongside progressive loss of cognition and function, dementia presents another important challenge, collectively referred to as behavioural and psychological symptoms of dementia (BPSD) or, alternatively, as neuropsychiatric symptoms in dementia or non-cognitive symptoms of dementia. Up to 80% of patients with dementia present with BPSD at some stage of their illness (Lyketsos et al., 2002). Presentations include psychiatric symptoms such as anxiety, depression, and psychotic features such as hallucinations and delusions, as well as behavioural issues such as agitation, aggression, disinhibition, hypersexuality, wandering, sleeping and eating problems, and motor symptoms (Cumming and Kleinberg, 1994).

The presence of BPSD is associated with impaired quality of life, and increased rate of institutionalization and cost of care with many people having to live in residential care settings such as long-term care homes (Seitz et al., 2010; Zuidema et al., 2010). When BPSD symptoms are severe, transfer to an inpatient setting may be the only option to allow adequate treatment. Thus, BPSD is a common problem on inpatient geriatric psychiatry units. Inadequately controlled BPSD may precipitate hospital admission by making it impossible for individuals to live at home with family members or in residential/nursing home settings. Furthermore, their emergence or persistence during an inpatient

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Table 1. Non-pharmacological treatments for agitation and aggression in Alzheimer's or mixed vascular dementia.

Category	Treatment
Social contact	Pet therapy, one to one visits
Sensory enhancement/relaxation	Hand massage, individualized music, individualized art, sensory modulation, multi-sensory environments (e.g. snoezelen)
Purposeful activity	Helping tasks/volunteer roles, inclusion in group activity programs, access to outdoors
Physical activity	Exercise groups, indoor/outdoor walks, individual exercise programs
Neurocognitive intervention technology	Therapeutic robot (e.g. Paro seal), tablet computer, gaming console
Caregiver interventions	Caregiver education, caregiver support, connection to external organizations and services

Note. This table is provided for reference only, an appraisal of the evidence base underpinning these treatment strategies and their suitability depending on behavioural and psychological symptoms of dementia (BPSD) severity is outside of the scope of this paper.

stay may prolong hospitalization and interfere with successful discharge. While BPSD may be associated with any form of dementia, this paper describes a drug treatment algorithm for agitation and aggression, specifically associated with Alzheimer's or mixed (Alzheimer's/vascular) dementia. It was originally designed for use by psychiatrists working in large teaching hospitals in Toronto and London, Ontario, Canada. While both pharmacological and non-pharmacological treatments have been reported to reduce BPSD symptoms, this paper addresses pharmacological treatments. For reference, non-pharmacological treatments which may be used alongside the drug treatments described here have been listed in Table 1.

Rationale for a treatment algorithm

Evidence for the efficacy of psychotropic drugs in BPSD associated with Alzheimer's and mixed dementia has emerged over the last two decades. Trials of varying quality along with meta-analyses, case series, and case reports now exist for various drugs in several classes. Yet, many of these drugs, such as antipsychotic medications, confer well-known risks of side effects and toxicity, especially in the elderly. Faced with this complex and evolving evidence, adopting a rational and consistent prescribing strategy is challenging.

In the Canadian context, there has been a reduction in antipsychotic drug prescription rates in the long-term care setting after a warning was issued by Health Canada in 2004 relating to risks of mortality and stroke in patients with dementia treated with antipsychotics (Vasudev et al., 2015). This reduction coincided with increased rates of exposure to two psychotropic drugs from two or more different classes ("polypharmacy"), and to drugs lacking an evidence of effectiveness. This suggests that greater direction is required in managing BPSD.

Appropriate algorithmic treatment has the potential to improve outcomes such as faster symptom control, decreased length-of-stay, lower rates of polypharmacy, and higher caregiver and patient satisfaction. Algorithmic treatment has been used successfully in the treatment of depression (Katon et al., 1995; Trivedi et al., 2004). A sequential drug treatment algorithm has been applied specifically to geriatric patients with depressive disorders (Mulsant et al., 2001). In updating their algorithm for treatment of geriatric depression, Mulsant et al. (2014) reaffirmed their view that algorithmic treatment using a sequential approach should lead to superior outcomes compared with individualized treatment, in that it allows standardization of the quantity and quality of drug treatment through, for example, optimizing drug dosing, the frequency of follow-up and the length of drug treatment trials. Existing algorithms for treatment of BPSD either address symptoms other than agitation and aggression (e.g. psychosis (Madhusoodanan and Ting, 2014)) or, where these symptoms are a focus (e.g. British Columbia BPSD Algorithm, 2014; Salzman et al., 2008), differ from the present algorithm in that they do not propose sequential treatment with a defined sequence of drugs with pre-specified dosing schedules and decision time-points.

Methods

An algorithm for management of agitation and aggression associated with Alzheimer's and mixed Alzheimer's/vascular dementia was devised by an inter-disciplinary team consisting of psychiatrists, nurses, occupational and recreational therapists, and managers. The current paper describes only the segment of the algorithm on pharmacological treatments, which was designed by the psychiatrists. The intention was to produce an algorithm that could be used after a period of drug washout and baseline assessment. This algorithm consists of a series of drugs to be used sequentially in monotherapy over six steps. Dosing schedules have been generated for each drug, which cater both to patients of normal constitution and those deemed "frail" because of their constitution or medical co-morbidity. The schedules were designed to provide decision points at which drugs could be held at the existing dose or titrated depending on observed response. In addition to the main sequential algorithm, we provide guidance on: washing out existing psychotropic drugs at the start of the process; drugs that may be used on a *pro re nata* (PRN) basis (e.g. trazodone and lorazepam); and the role of cholinesterase inhibitors and memantine (Figure 1).

For the main algorithm, drug treatments were appraised by the psychiatrists from participating institutions using the following five criteria, listed in order of importance (Figure 2); (a) strength of evidence of efficacy in agitation or aggression in Alzheimer's or mixed Alzheimer's and vascular dementia; (b) time to onset of clinical effect; (c) tolerability/side effect profile; (d) ease of use (e.g. propensity to drug interactions); and (e) efficacy of the drug or class for other relevant conditions beyond BPSD (e.g. anxiety disorders)

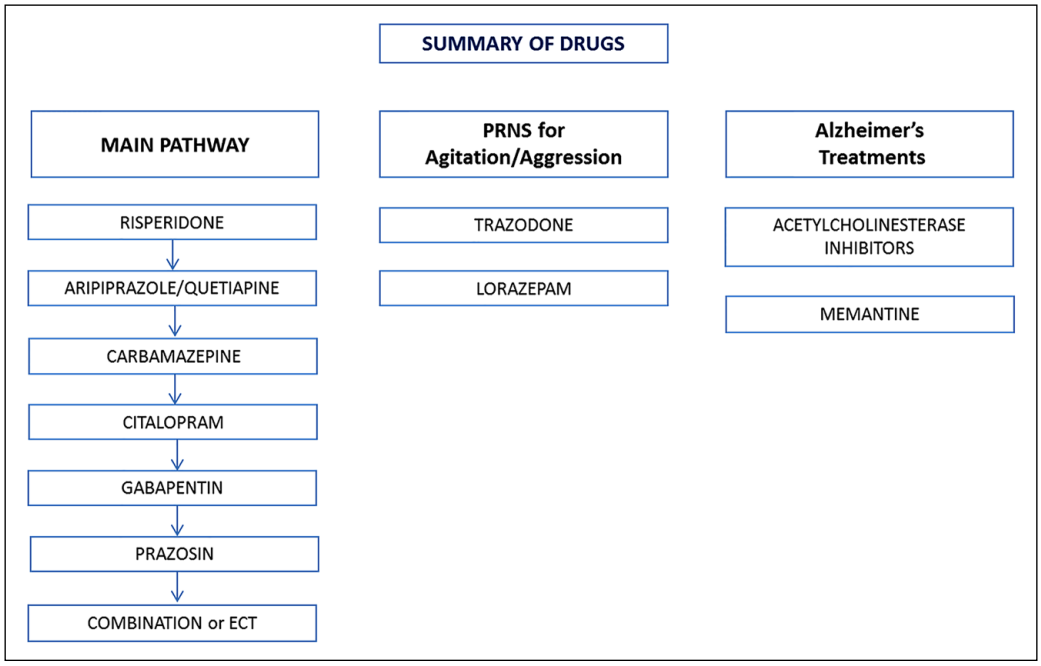

Figure 1. Summary of drugs, illustrating main pathway, *pro re nata* (PRN) drugs and Alzheimer's disease treatments. ECT: electroconvulsive therapy.

	STEP	EFFICACY	TIME TO ONSET	TOLERABILITY	EASE OF USE	EFFICACY/ OTHER
RISPERIDONE	1					
QUETIAPINE	2					
ARIPIPRAZOLE	2					
CARBAMAZEPINE	3					
CITALOPRAM	4					
GABAPENTIN	5					
PRAZOSIN	6					

Figure 2. Assessment of sequential drug treatment algorithm medications in five domains.
Key: Five domains are listed in descending order of importance in their contribution for ranking the drugs in the sequential medication algorithm. Efficacy: strength of evidence for efficacy in agitation/aggression in Alzheimer's or mixed Alzheimer's/vascular dementia. Time to onset: time to onset of clinical effect. Tolerability: tolerability/side effect profile. Ease of use: potential for interactions/disruption of co-prescribed medication. Efficacy/other: evidence in other relevant conditions beyond behavioural and psychological symptoms of dementia (BPSD), including anxiety disorders. Green indicates that the drug was given the highest rating, yellow intermediate rating and red the lowest rating. For instance, risperidone is rated "green" for efficacy due to the existence of multiple successful randomized trials, while gabapentin is rated "red" as evidence relies on case reports/case series only. The remaining drugs are rated "yellow" or intermediate on efficacy since positive randomized controlled trials are more limited, or evidence is based on meta-analysis of randomized trials.

Results

Drugs and physical treatments included in the main sequential treatment algorithm – evidence and rationale

Following review of patient's suitability for the algorithm, baseline assessments, and a "clean-up" or "washout" period (Figure 3), the algorithm begins with trials of antipsychotic drugs (Figure 4). Azermaia et al. (2012) systematically appraised existing guidelines for BPSD. They noted that there was a broad agreement among 15 clinical guidelines that antipsychotic drugs had the strongest evidence for treating BPSD. However, the efficacy of antipsychotic drugs comes at a cost for some individuals, as they carry risks of falls, excessive sedation, and metabolic abnormalities (Schneider et al., 2006). A further concern is the reported increased risk of stroke and mortality associated with atypical antipsychotics (Schneider et al., 2005). In general, guidelines recommend restricting the use of antipsychotic medications to where symptoms and their potential consequences meet specific criteria. For example, recent guidance from the American Psychiatric Association states "… nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe,

A 10 day period is allowed for drug clean up (and behavioural assessment)

1) COGNITIVE ENHANCERS (AchEIs or Memantine) should NOT be discontinued unless there is clear evidence that their introduction may have caused the BPSD episode (e.g. Frontal variant of Alzheimer's)

2) For the Following Drugs... ANTIPSYCHOTICS, ANTIDEPRESSANTS (including TRAZODONE), CARBAMAZEPINE, GABAPENTIN, PRAZOSIN, CYPROTERONE ACETATE

- DISCONTINUE IF DRUG WAS STARTED SPECIFICALLY FOR BPSD (i.e. Based on HISTORY and CLINCIAN'S DISCRETION, DO NOT DISCONTINUE IF DRUG WAS STARTED FOR ANOTHER CLINICAL INDICATION such as treatment of Depression, Bipolar Disorder, Affective Psychosis, Schizophrenia etc.)
- WHERE DISCONTINUATION REQUIRED, IT SHOULD BE UNDERTAKEN FROM DAY 3-DAY 10

3) For the Following Drugs .... BENZODIAZEPINES, ZOPICLONE (and other Z-DRUGS)

- DISCONTINUE UNLESS CLEAR RECENT EVIDENCE OF INSURMOUNTABLE DIFFICULTY IN STOPPING
- WHERE DISCONTINUATION INDICATED, IT SHOULD BE UNDERTAKEN AS SLOWLY AS NEEDED FOR SAFETY (therefore may continue down-titration process beyond 10 days).

4) During Clean up period, may use PRN PSYCHOTROPIC DRUGS AS FOLLOWS

a) TRAZODONE : can be used 25 mg every hour as needed, initial maximum set at 150mg/24hours, may be increased at prescriber discretion to 300mg in 24 hours in non-FRAIL patients. NOTES: helpful as inducer of sleep but could cause paradoxical agitation in some patients due to anxiogenic metabolite, watch for falls, hypotension and excessive sedation

b) BENZODIAZEPINES (use lorazepam 0.5 mg every 4 hours as needed, max 2 mg/24 hours).

- While a PRN benzodiazepine drug can be helpful to allow procedures such as imaging and activities such as dental visits to take place, it may cause agitation and disinhibition, in particular in those with frontal deficits, therefore patients should be assessed for risks of falls and excessive sedation.

Figure 3. Drug clean-up principles.
AchEI: acetycholinesterase inhibitor; BPSD: behavioural and psychological symptoms of dementia; PRN: *pro re nata*.

are dangerous, and/or cause significant distress to the patient" (American Psychiatric Association, 2016: 24). However, in the hospital inpatient setting for which the algorithm was designed, many patients with dementia exhibiting agitation and aggression do indeed meet these criteria, for example being at significant risk of harming themselves or others and exhibiting clear evidence of distress. Where symptoms of agitation and aggression do not meet these criteria, this drug treatment algorithm should not be used.

While the recommended treatment sequence begins with antipsychotic agents, we have acknowledged that a minority of patients or their families and caregivers may not agree with the use of antipsychotic drugs, in which case drug treatment may need to start lower down the algorithm at Step 3. While several antipsychotic drugs have trial or meta-analytic evidence of efficacy for agitation and aggression associated with Alzheimer's disease (Seitz et al., 2013), we selected three atypical antipsychotic drugs: risperidone, quetiapine, and aripiprazole.

Step 1: risperidone. Risperidone (neuroscience based nomenclature (NbN): dopamine, serotonin, noradrenaline receptor antagonist (Nutt and Blier, 2016)) has the strongest evidence base for treatment of BPSD symptoms in Alzheimer's or mixed dementia through several large randomized trials (Brodaty et al., 2003; De Deyn et al., 1999; Durán et al., 2005; Schneider et al., 2006; Suh et al., 2006). In Canada, risperidone has approval for symptomatic management of aggression or psychosis restricted to severe dementia of the Alzheimer's type (Health Canada, 2015) while in the UK it is licensed for short-term treatment of aggression in BPSD (up to six weeks). In the USA, the use of risperidone is not approved for any BPSD-related indication.

As all antipsychotics, risperidone carries cardiovascular and metabolic risks. A relationship between antipsychotics and stroke has been suggested (Herrmann and Lanctôt, 2005). In a large retrospective case-control study of patients with dementia, antipsychotics conferred an excess risk of mortality from all causes over 180 days, compared with matched controls on no psychotropic drug treatment (Maust et al., 2015) with a number needed to harm (NNH) of 27 for risperidone (95% confidence interval: 19–46). Olanzapine and quetiapine had slightly, but not significantly, higher NNHs but the risk of mortality for all three atypical antipsychotics studied had a significant relationship to dose. Thus, the algorithm allows for the scenario that a patient or their caregivers may be unwilling to agree to the use of atypical

antipsychotics, whereby the medication algorithm may be started at Step 3.

Step 2(a): quetiapine. The evidence base for quetiapine (NbN: dopamine and serotonin receptor antagonist and noradrenaline reuptake inhibitor) is considerably weaker than that for risperidone. However, a meta-analysis (Cheung and Stapelberg, 2011) combining five randomized trials reported a statistically significant effect relative to placebo on neuropsychiatric symptoms (Neuropsychiatric Inventory scores (Cummings et al., 1994)) and overall improvement (Clinical Global Impression (CGI) scores). While these effects were modest, quetiapine ranked well for time to onset of effect with CGI change score reported to be significantly greater than placebo after one week (Zhong et al., 2007), tolerability, and its evidence of efficacy in other disorders such as Generalized Anxiety Disorder (for review see Baldwin et al., 2014). Quetiapine was therefore included alongside aripiprazole as an option for the algorithm's second step.

Step 2(b): aripiprazole. Again, aripiprazole (NbN: dopamine, serotonin receptor partial agonist) has a smaller evidence base than risperidone. However, there is randomized trial evidence suggesting a statistically significant effect for agitation in patients with Alzheimer's disease where BPSD symptoms included psychosis (Mintzer et al., 2007), with superiority over placebo detected as early as week 2 for some outcomes. Aripiprazole was superior to placebo in a meta-analysis (Schneider et al., 2006), both on outcome measures specific to agitation and on the more wide-ranging Neuropsychiatric Inventory. Aripiprazole was included as an alternative to quetiapine due to its differing mechanism of action, which involves partial D2 receptor antagonism. Although this has not been demonstrated, the panel of psychiatrists believed this different mechanism of action might confer a greater efficacy in risperidone non-responders than the remaining atypical antipsychotics.

Step 3: carbamazepine. Carbamazepine (NbN: glutamate: voltage-gated sodium and calcium channel blocker) is used in many forms of epilepsy and as a mood stabilizer for bipolar disorder. Case reports support its use to control aggressive outbursts in episodic dyscontrol syndrome (Lewin and Sumners, 1992). The panel ranked carbamazepine below the antipsychotics. It has one successful but small randomized trial (Olin et al., 2001) in patients with BPSD who were resistant to treatment with antipsychotics, with efficacy demonstrated over a six-week treatment period, but also several other negative trials in BPSD (for review see Konovalov et al., 2008). Carbamazepine presents several issues to prescribers including potential for drug interactions given its known induction of the CYP 3A4 enzyme, which plays a role in the metabolism of numerous psychotropic drugs (Davies et al., 2004), and rare but potentially dangerous side effects including severe skin reactions, aplastic anemia and agranulocytosis. However, the panel considered carbamazepine as a drug that still had potential for efficacy in the psychopathology of BPSD within a short time-scale in patients resistant to or unable to take antipsychotics. By Step 3 patients may already have been hospitalized for six weeks or more, and in Ontario, patients admitted to an inpatient psychiatric unit may be forced to relinquish their place in long-term care homes after 60 days in hospital. Thus, the panel regarded it as essential that prescribers had the option around this deadline of using a drug with the potential to deliver a marked improvement within a few weeks, in at least a minority of cases. However, prescribers can skip steps in the algorithm, and when they consider carbamazepine unsuitable, they may move straight to Step 4, citalopram.

Step 4: citalopram. Citalopram (NbN: serotonin reuptake inhibitor) is a selective serotonin reuptake inhibitor (SSRI) antidepressant. SSRIs are the most widely used antidepressants and also have efficacy for most anxiety disorders (Baldwin et al., 2014). The use of citalopram in BPSD has various pros and cons. In favor of the inclusion of citalopram is the recent successful placebo-controlled randomized trial known as "CitAD" in which citalopram titrated to a target of 30 mg/day was effective in reducing BPSD symptoms (Porsteinsson et al., 2014) and three previous trials (Pollock et al., 1997, 2002, 2007). Against the use of citalopram are the recent concerns of QTc prolongation which prompted the US Food and Drug Administration and Health Canada to restrict its use to a maximum of 20 mg/day in people aged over 65 years (Health Canada website, 2012). There is also the possibility that despite the data from the CitAD trial, treatment with SSRIs may initially cause increased agitation through jitteriness/anxiety syndrome (Sinclair et al., 2009). A recent analysis of CitAD data (Weintraub et al., 2015) concludes that at least nine weeks are required for full response with citalopram. Thus, in the time-sensitive context of treatment of BPSD in inpatient settings, the panel consensus was that prescribers should have the option of undertaking a trial of carbamazepine, for which both benefits and adverse effects may be realized more quickly, before a trial with citalopram.

The panel considered a variety of pharmacologic agents for possible fifth and sixth steps (see below), given that some or all of the standard agents recommended for the first four steps may not be appropriate, for example through issues relating to consent, or previous intolerance to one or more of the recommended drugs prior to being admitted to an inpatient unit. It selected two agents that have different mechanisms of action: gabapentin and prazosin.

Step 5: gabapentin. Originally developed for treatment of epilepsy, gabapentin (NbN: glutamate: voltage-gated calcium channel blocker) has only case reports and case series suggesting effectiveness for BPSD symptoms, covering agitation and aggression, with or without sexual disinhibition (Kim et al., 2008). It was included at this point in the medication algorithm due to its versatility in treating allied conditions such as anxiety disorders (Baldwin et al., 2014), its lack of potential cytochrome P-450-based pharmacokinetic interactions (since it is excreted unchanged by the kidney), and good tolerability. Some case reports indicate a relatively rapid time to onset of effect, within two weeks (Cooney et al, 2013) although this remains to be assessed in a randomized placebo-controlled trial.

Step 6: prazosin. Prazosin (NbN: noradrenaline receptor antagonist) is an alpha-adrenoceptor blocking drug originally used as an antihypertensive. It has more recently been used in psychiatry to reduce distressing dreams of post-traumatic stress disorder (De Berardis et al., 2015). Prazosin has one small randomized placebo controlled trial reporting a significant impact on agitation and aggression in Alzheimer's dementia using doses

between 1 mg and 6 mg/day (Wang et al., 2009). It should be avoided in individuals who have experienced postural hypotension, and it is advised to give the first dose at bedtime to reduce the impact of hypotensive effects.

Step 7(a): combination of any two drugs which have produced partial response, or Step 7(b): electroconvulsive therapy (ECT). ECT is included at the last treatment step in the algorithm. A recent review of studies in which ECT was given to people having a mood disorder in the presence of dementia did not identify clear evidence of excess safety risks compared with non-demented individuals. However, data was acknowledged to be limited with some suggestions of cognitive decline in late stage dementias or in vascular dementia (Oudman, 2012), necessitating careful discussion with patients (where possible) and family members. Although there are no published controlled trials of ECT in BPSD, rapid resolution of agitation and aggression has been reported in small case series (Carlyle et al., 1991; Grant and Mohan, 2001) and safety and efficacy has been documented in two retrospective case note reviews (Isserles et al., 2017; Ujkaj et al., 2012). Isserles et al. (2017) report a clinically meaningful response of BPSD in 72% of cases, with maintenance ECT sustaining the response in 87%, but all observations were uncontrolled.

Drugs included for PRN use – evidence and rationale

While the above sections describes steps the panel endorsed for sequential treatment of agitation and aggression in Alzheimer's and mixed Alzheimer's/vascular dementia, it was recognized that at times the regular treatments cannot offer adequate protection from the impact of these symptoms. Accordingly, the algorithm allows for the possibility of supplementing medication given in the main sequence with drugs to be given on a PRN basis. The main drug selected for this purpose was trazodone, with use of lorazepam considered acceptable in certain circumstances.

PRN drug 1: trazodone. Trazodone (NbN: serotonin receptor antagonist and receptor agonist) is an effective antidepressant. Although it was developed and entered the market concurrently to tricyclic agents such as clomipramine, desipramine, and nortriptyline, it differs markedly from these drugs in its mechanism of action and receptor binding profile. Its main antidepressant action is thought to be through direct blockade of certain serotonin receptors while weak serotonin reuptake inhibition and receptor agonism are adjunctive effects. It lacks affinity for cholinergic receptors (thereby avoiding many of the unwanted side effects associated with tricyclics) but does produce a strong histaminergic effect which directly promotes sedation. There is some evidence to suggest that this sedating effect may be responsible for reducing irritability and agitation (López-Pousa et al., 2008) although this evidence was deemed too limited in a Cochrane review to merit recommendation for routine use (Martinón-Torres et al., 2004). Still, given this limited evidence and more than 20 years of experience with the use of trazodone to promote sedation in patients with dementia (Houlihan et al., 1994) and its generally good tolerability, trazodone was selected as the PRN drug of choice.

PRN drug 2: lorazepam. Benzodiazepines (NbN: positive allosteric modulators, gamma-aminobutyric acid (GABA)-A receptor, benzodiazepine site) have been widely used as anxiolytic and sedative/hypnotic agents since their introduction 50 years ago (Baldwin et al., 2013). However, they have been associated with falls and fractures (Cumming and Le Couteur, 2003), and acute cognitive deficits, especially in the elderly (Foy et al., 1995; Tannenbaum et al., 2012). Benzodiazepines are also associated with tolerance and addiction. For these reasons the panel chose not to recommend benzodiazepines in the sequence of regular treatments. Nevertheless, it concluded that occasional use of the benzodiazepine lorazepam as a PRN drug was acceptable in cases of extreme agitation or aggression where behavioural interventions and trazodone are ineffective, or when brief stressful circumstances might exacerbate or induce agitation and aggression, for example, medical tests or dental procedures.

Drugs not included (in alphabetical order), the evidence and the rationale for non-inclusion

Amisulpiride (NbN: dopamine receptor antagonist). This drug was not included as it is unavailable in Canada and the USA, despite being widely used for psychotic disorders in many other countries. Evidence of efficacy in BPSD is limited to open studies (Lim et al., 2006; Mauri et al., 2006).

Cyproterone acetate. Evidence supports the use of cyproterone for hypersexuality. There is also some evidence for agitation and aggression when hypersexuality is not a factor from one randomized double bind trial (Huertas et al., 2007) and one meta-analysis (Bolea-Alamanac et al., 2011). However, in terms of adverse effects, cyproterone has the potential to cause osteoporosis, raised liver enzymes, and a small increase in the risk of thrombosis. For these reasons cyproterone acetate was not included in the algorithm.

Diphenhydramine. A small double-blind randomized trial (Coccaro et al., 1990) suggested that this antihistaminergic agent may have similar efficacy to haloperidol in treating behavioural symptoms in severe dementia. However it has many potential adverse effects, including those arising from its anticholinergic properties. Taking this together with the limited evidence base for efficacy meant that diphenhydramine was not selected for inclusion.

Estrogen. There have been two randomized placebo controlled trials involving estrogen in BPSD, one using transdermal patches (Hall et al., 2005) which did not report any benefit, and one using oral conjugated estrogen which reported a significant benefit over placebo in the eight patients randomized to the drug (Kyomen et al., 1999). However, the type of dementia was not stated. Overall it was felt that the evidence base for estrogen was not sufficiently developed to merit inclusion in the algorithm.

Haloperidol (NbN: dopamine receptor antagonist). Evidence exists for haloperidol in BPSD with a 2002 Cochrane review suggesting that its utility was limited to aggression (Lonergan et al., 2002). In a subsequent study, improvement in

BPSD ascertained by the Cohen-Mansfield Agitation Inventory was equivalent to that associated with olanzapine (Verhey et al., 2006). However, the panel was reluctant to recommend a conventional antipsychotic in an algorithm where patients may first have been prescribed two atypical antipsychotics. This view was motivated by safety concerns. Although a recent study (Maust et al., 2015) reported that the NNH with haloperidol, for the outcome of mortality, was similar to risperidone, one large retrospective study of nursing home residents with dementia reported a significantly higher hazard ratio for all-cause mortality for new users of haloperidol compared with atypical antipsychotics (Liperoti et al., 2009). In another cohort study where a diagnosis of dementia was not required for inclusion, conventional antipsychotics significantly increased risk both of death and femur fracture in nursing home residents compared with atypicals (Huybrechts et al., 2011).

Memantine (NbN: glutamate receptor antagonist). This modulator of glutamatergic neurotransmission via N-methyl-D-aspartate receptor (NMDA) receptor antagonism has evidence from a meta-analysis of a positive effect in agitation and aggression (Grossberg et al., 2009), but the observed difference was apparent only after six months of treatment. A further pooled analysis reported a benefit observable from 12 weeks (Wilcock et al., 2008). These analyses suggest that onset may be too slow to address acute behavioural disturbances in the inpatient setting. A more recent randomized trial suggested that in patients taking rivastigmine, addition of memantine conferred limited benefit in behavioural symptoms compared with placebo (Howard et al., 2012). Although neither memantine nor the acetylcholinesterase inhibitors have been included as treatment steps in the algorithm per se, are all purported to be effective treatments for temporarily slowing the general progression of Alzheimer's disease, and should be retained and if necessary dose-optimized for this purpose in parallel with the main algorithm.

Olanzapine (NbN: dopamine and serotonin receptor antagonist). This antipsychotic was not included in the treatment sequence due to concerns relating to its metabolic profile and anticholinergic properties relative to the three atypical antipsychotic drugs that are included (Chew et al., 2008; Mulsant et al., 2004). Olanzapine has double-blind randomized trial evidence for BPSD in Alzheimer's dementia (Street et al., 2000), but a meta-analysis (Schneider et al., 2006) of this and two other trials reported no difference from placebo on either measures specific to agitation or more general measures of neuropsychiatric symptoms.

Oxcarbazepine (NbN: glutamate: voltage-gated sodium and calcium channel blocker). This drug has similar pharmacology to carbamazepine. However carbamazepine was preferred for inclusion in the algorithm since for oxcarbazepine, evidence relating to agitation and aggression in Alzheimer's/mixed/vascular dementia is limited to one placebo-controlled trial (Sommer et al., 2009), which reported only a non-significant trend in favor of the drug.

Propanolol. This beta-blocking agent is sometimes used to address physical symptoms associated with anxiety, although evidence of effectiveness is limited (Steenen et al., 2016). It has one successful placebo controlled trial illustrating a reduction in BPSD in Alzheimer's disease (Peskind et al., 2005). However, it was not included, in part due to concerns that its antihypertensive and cardiac slowing effects may compromise cardiovascular function in some individuals. Peskind et al. acknowledged these limitations as restricting the drug's utility in the population studied.

Sertraline (NbN: serotonin reuptake inhibitor). Among selective serotonin reuptake inhibitors, sertraline has an advantage over citalopram in having no known association with QTc prolongation. However, while citalopram has been investigated thoroughly in large scale randomized trials (both against placebo and against antipsychotics), sertraline's evidence in treating agitation and aggression in BPSD is limited to one small randomized trial (n=13) in which it was compared against haloperidol (Gaber et al., 2001). There was no significant difference in Cohen-Mansfield Agitation Inventory score from baseline to the end of the study period at 10 weeks. We cannot therefore be certain that sertraline is as effective as citalopram and as yet do not have sufficiently good evidence to conclude that citalopram's efficacy is derived from a class effect that would be common to all SSRIs. For this reason sertraline was not included.

Tetrahydrocannabinol. Little evidence was available on cannabinoids in BPSD at the time of review and they were not included in the algorithm. Subsequently a retrospective chart review (Woodward et al., 2014), suggested the isomer dronabinol may have benefits against agitation and aggression in BPSD. In contrast, a randomized controlled trial has found no evidence of benefit for tetrahydrocannabinol in agitation or aggression in BPSD compared with placebo (van den Elsen et al., 2015).

Valproate (NbN: glutamate: mechanism yet to be determined). This antiepileptic and mood-stabilizing agent was excluded from the algorithm due to lack of efficacy for agitation and aggression in dementia (Konovalov et al., 2008; Schneider et al., 2006), and safety concerns.

Clinical use of the algorithm

In determining eligibility for entering the algorithm, it is essential to search for and rule out any medical cause for agitation and aggression. This includes the need to address pain management, as agitation and aggression in dementia often occur as a response to pain. Note that a randomized placebo cross-over trial examining the effects of giving 3 g/day acetaminophen (paracetamol) for agitation and aggression in dementia irrespective of the presence or absence of reported pain, did not find any reduction in agitation with this analgesic agent compared with placebo (Chibnall et al., 2005). However, another trial which employed a pain specialist to assess and select the most appropriate analgesic medication from four options reported significant benefits over treatment as usual especially in the domain of verbal aggression (Husebo et al., 2014). We therefore recommend assessment of pain and appropriate management where it is suspected, but do not advocate any one specific analgesic medication to be given universally to all patients with agitation and aggression in dementia.

Table 2. Assessments to be undertaken at baseline, end of clean-up period, at drug prescription decision points or drug changes, and at exit from the pathway.

	Baseline assessments (at entry)	End of clean-up period	Decision points/dose changes	Exit
BPSD symptoms and cognitive assessments				
Neuropsychiatric Inventory (NPI-Q)	✓	✓	✓	✓
CGI-Severity	✓	✓	✓	✓
CGI-Improvement (from baseline/entry)		✓	✓	✓
CMAI	✓			✓
MOCA	✓			✓
Dementia-FAST	✓			✓
Motor assessments				
AIMS	✓			✓
SAS	✓			✓
BAS	✓			✓
Cardiac and metabolic assessments				
ECG	✓			✓
Blood count[a]	✓			✓
Electrolytes	✓			✓
Urea[b]/creatinine	✓			✓
Blood glucose	✓			✓
Lipid profile	✓			✓

AIMS: Abnormal Involuntary Movements Scale; BAS: Barnes Akathisia Scale; BPSD: behavioural and psychological symptoms of dementia; CGI: Clinical Global Impression; CMAI: Cohen Mansfield Agitation Inventory; ECG: electrocardiogram; FAST: Functional Assessment Staging Tool; MOCA: Montreal Cogntive Assessment; SAS: Simpson Angus Scale.

[a]Known as complete blood count (CBC) in North America and full blood count (FBC) in other English-speaking settings.

[b]Known as blood urea nitrogen (BUN) in North America.

Patients with dementias other than Alzheimer's or mixed Alzheimer's/vascular dementia should not be entered into the present algorithm, nor should those where symptoms of agitation and aggression are not present or there is judged to be no elevated risk to the patient or others and an absence of marked distress. For those who are eligible, we recommend the instigation of non-pharmacological strategies first and then alongside drug treatment, but their discussion is beyond the scope of this manuscript.

For all patients entering the algorithm, a period of 10 days is allocated for assessment and clean up/washout of existing medications (Figure 3). Standard baseline assessments to be performed before the clean-up phase (Table 2) include the Neuropsychiatric Inventory (NPI-Q), the Clinical Global Impression-Severity (CGI-S), Barnes Akathisia Scale (BAS), Abnormal Involuntary Movements Scale (AIMS) and Simpson Angus Scale (SAS), Cohen-Mansfield Agitation Inventory (CMAI), Montreal Cognitive Assessment (MOCA), and Dementia Functional Assessment Staging Tool (FAST) test. Where possible, QTc should be ascertained by an electrocardiogram (ECG), as several of the suggested drugs can cause QTc prolongation and knowledge of an already prolonged or borderline QTc may lead to skipping some of the steps. Standard blood tests (complete blood count (CBC), electrolytes, creatinine/blood urea nitrogen (BUN), blood glucose and lipid profile) are recommended at entry.

Clean-up phase. The clean-up phase (Figure 3) follows the following principles:

1. Cognitive enhancers (acetylcholinesterase inhibitor or memantine) should not be discontinued unless there is evidence that their introduction may have caused the BPSD symptoms (e.g. as may occur in the frontal variant of Alzheimer's disease). Optimization of these drugs is a parallel process to initiation of drugs specifically for treatment of agitation and aggression in BPSD and is therefore not part of the main drug treatment pathway. However, it is recommended that while working through the main pathway prescribers should avoid introducing new acetylcholinesterase inhibitors or memantine to permit assessment of the effects of pathway drugs.
2. Antipsychotics, antidepressants (including trazodone), carbamazepine, gabapentin, prazosin and cyproterone acetate should be discontinued if these drugs had been started specifically for BPSD, but not if started for another clinical indication (e.g. depression, schizophrenia). Where discontinuation is required, this should be undertaken from day 3 to day 10.
3. Benzodiazepines or "Z-drugs" (e.g. zopiclone, zolpidem) should be discontinued unless there is clear recent evidence of insurmountable difficulty in stopping them. Where discontinuation is indicated, it should be undertaken as slowly as needed for safety, which in many cases will necessitate a gradual taper with the down-titration process continuing beyond day 10.
4. During the clean-up period (and afterwards), the PRN psychotropic drugs described in the section on 'Drugs included for PRN use' above may be used, either (a) trazodone 25 mg every hour as needed, maximum initially 150 mg/24 h with option to increase to a maximum of 300 mg/day if required in non-FRAIL patients, or

(b) lorazepam 0.5 mg as needed, max 2 mg/24 h. As per above, trazodone is the preferred choice whereas lorazepam is recommended only in specific circumstances.

At the end of the clean-up phase, Clinical Global Impression-Improvement (CGI-I) (compared with baseline), CGI-S and NPI-Q are performed (Table 2). In a substantial minority of cases, the clean-up phase in an inpatient setting may produce adequate improvement (normally reflected through a CGI-I score of one or two), obviating the need to enter the main drug treatment pathway.

Main pathway of sequential drug treatment (Figure 4 and Tables 3 and 4). We acknowledge that some patients or their carers/decision makers may have issues with the use of antipsychotic drugs. These medications have the potential to provide rapid reduction not only agitation and aggression, but also psychosis, and they have the strongest evidence base for efficacy of all the drugs included in the pathway. However, they also carry risks of mortality and morbidity including stroke, falls and fractures, QTc prolongation, pneumonia and metabolic issues. Therefore, when antipsychotics are not permissible, the medication algorithm (Figure 4, Table 3) should be started at Step 3. Otherwise, physicians should start by considering Step 1 which is risperidone. If it is decided to skip Step 1 and not to use risperidone, one of the Step 2 drugs, quetiapine or aripiprazole, may be selected. Similarly subsequent drugs or steps may be skipped if a proposed drug is deemed inappropriate by the prescriber, for example when there is clear evidence of previous intolerance. Dosing schedules of recommended drugs are available in Tables 3 and 4. These schedules indicate the starting dose, time-points of dose increases, and "decision points" where the choice must be made of increasing the dose, exiting the pathway in the case of successful treatment, or switching to the next drug. For the first five drugs tabulated, a dosing schedule involving lower doses is available when the patient is deemed to be "frail". There is no operationalized definition of frailty, but it can be established based on (a) body mass index (BMI)/weight, (b) vital signs, (c) mobility, and (d) comorbid conditions and concurrent medications. For gabapentin and prazosin, dosing and the pace of dose increases should take account of further factors: renal function for gabapentin and both renal and hepatic function, along with the presence of antihypertensive agents, for prazosin. For this reason, specific "frail" dosing schedules are not provided for these final two drugs.

Decision points (shaded orange or red in the dosing schedule, Tables 3 and 4) occur when the patient has been taking the drug at the initial target dose for 7–14 days and at the end of a 21-day trial (or the end of a 21-day extension). At these points CGI-I (compared with baseline), CGI-S and NPI-Q are repeated. Where the patient is "much improved" or "very much improved" (CGI-I score two or one), the treatment is considered successful. The patient can exit the algorithm and continue the effective dose as a maintenance treatment, with reviews at regular intervals in line with existing treatment guidelines (Health Quality Ontario, 2016; Hogan et al., 2008). Otherwise (i.e. CGI-I from baseline=3 or more) at intermediate decision points (squares shaded orange), the dose should be increased up to the final target at day 21. At day 21 of a drug trial (squares shaded orange or red), CGI-I scores of four or more mean that the trial is unsuccessful and the patient should be switched to a different drug. It is usually the drug of the next step if that is considered appropriate but remembering to first reconsider medications in the sequence that were skipped in case they could now be appropriate.

At day 21, when a CGI-I score of three (minimal improvement) is recorded, in the case of risperidone and quetiapine only (decision squares shaded red), an extension of up to 21 days may be initiated with a further "intermediate decision point" at day 28 or 29. For all other drugs, a score of three is considered an unsuccessful trial. For risperidone and quetiapine after an extension, CGI-I scores of three or more at day 42 mean that the trial has been unsuccessful and the patient should be switched.

Clinicians should monitor for drug side effects as per their usual practice. Any pathway drug may be stopped at any time if it cannot be tolerated, moving to the next appropriate drug. The algorithm specifies that a third antipsychotic may be tried with whichever of aripiprazole or quetiapine was not initially selected in Step 2, if full trials of the first two antipsychotics could not be tolerated. The drugs outlined earlier as being included for PRN use, trazodone, and in certain circumstances, lorazepam, may be administered alongside the main pathway drugs where appropriate, using the same doses and regimens described for the clean-up phase.

Exiting the pathway. At exit, all assessments undertaken at baseline, along with the CGI-I score (relative to baseline), should be repeated. The ECG and blood tests should also be repeated at or within five days of the time of exit.

Implementation

The medication algorithm for agitation or aggression in Alzheimer's or mixed dementia has been implemented at several sites in Ontario, including inpatient facilities within large academic centers in Toronto or those serving smaller populations outside major cities. It was first introduced on the geriatric psychiatry inpatient units at the Centre of Addiction and Mental Health in Toronto. They now have three years of clinical experience of following the recommended steps of drug sequencing and dosing. During this period, it has been applied in the treatment of eligible patients. Medical centers in other Canadian provinces are currently considering adopting the algorithm. The applicability of the algorithm, allowing for any necessary modifications based on context, will also be examined in long-term care settings. Data are being collated centrally which will provide opportunities for registry-based research. These data will permit a thorough evaluation of the benefits of algorithmic treatment relative to "usual care," in terms of treatment outcomes such as symptomatic reduction, length of stay, and psychotropic drug polypharmacy.

Discussion

We speculate that treatment of inpatients experiencing agitation and aggression associated with Alzheimer's or mixed dementia may be improved by bringing structure and consistency to an area where numerous putative drug treatments exist but most trials have been published relatively recently. Even when physicians familiarize themselves with which drugs are the most appropriate, they may not necessarily adopt evidence-informed dosing

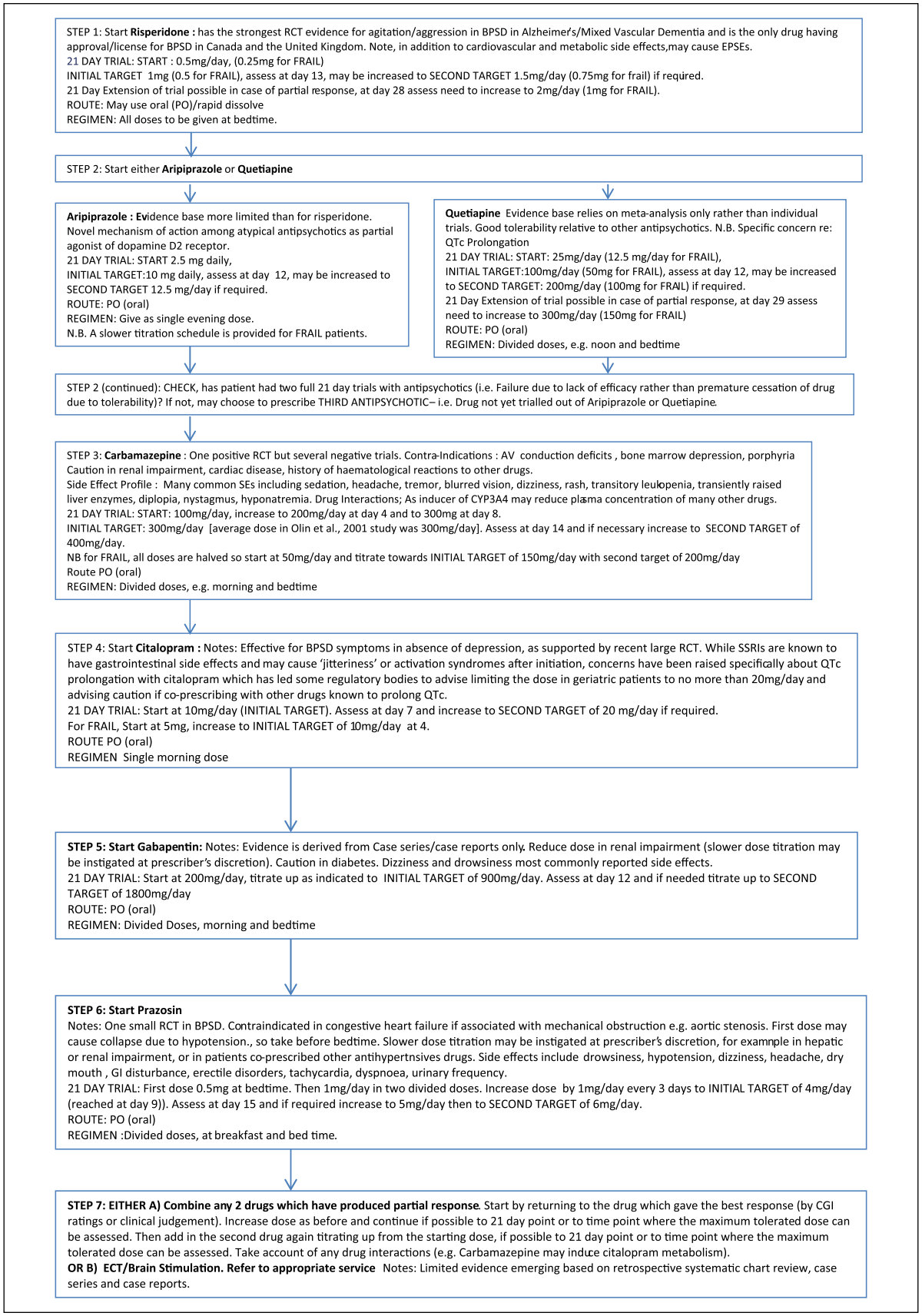

Figure 4. Flow chart illustrating sequential medication algorithm.
AV: atrioventricular; BPSD: behavioural and psychological symptoms of dementia; CGI; Clinical Global Impression; ECT: electroconvulsive therapy; EPSE: extrapyramidal side effect; PO: per os (oral); RCT: randomized controlled trial; SE: side effect; SSRI: selective serotonin reuptake inhibitor.

Table 3. Behavioural and psychological symptoms of dementia (BPSD) (agitation/aggression) in Alzheimer's or mixed dementia; drug and dosing schedules.

	Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	Risperidone	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Single evening dose																						
	Risperidone (frail)	0.25	0.25	0.25	0.25	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
	Single evening dose																						
2(a)	Aripiprazole	2.5	2.5	5	5	7.5	7.5	10	10	10	10	10	10	10	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
	Single evening dose																						
	Aripiprazole (frail)	1	1	2.5	2.5	2.5	2.5	5	5	5	5	7.5	7.5	7.5	7.5	7.5	10	10	10	10	10	10	10
	Single evening dose																						
2(b)	Quetiapine[a]	25	25	50	50	75	75	100	100	100	100	100	100	100	150	150	150	200	200	200	200	200	200
	Divided doses (i.e. start at 12.5 mg b.i.d.)																						
	Quetiapine[a] (frail)	12.5	12.5	25	25	37.5	37.5	50	50	50	50	50	50	50	75	75	75	100	100	100	100	100	100
	Divided doses																						
3	Carbamazepine	100	100	100	100	200	200	200	200	300	300	300	300	300	300	300	400	400	400	400	400	400	400
	Always b.i.d. (i.e. start at 50 mg b.i.d.)																						
	Carbamazepine (frail)	50	50	50	50	100	100	100	100	150	150	150	150	150	150	150	200	200	200	200	200	200	200
	Always b.i.d.																						
4	Citalopram	10	10	10	10	10	10	10	10	20	20	20	20	20	20	20	20	20	20	20	20	20	20
	Single morning dose																						
	Citalopram (frail)	5	5	5	5	10	10	10	10	10	10	10	15	15	15	15	15	20	20	20	20	20	20
	Single morning dose																						
5	Gabapentin[b,c]	200	200	400	400	600	600	900	900	900	900	900	900	900	1200	1200	1500	1500	1800	1800	1800	1800	1800
	Divided doses (i.e. start 100 mg b.i.d.)																						
6	Prazosin[d]	0.5	1	1	2	2	2	3	3	3	4	4	4	4	4	4	5	5	6	6	6	6	6
	First dose=0.5 mg at bedtime, divided into b.i.d. thereafter																						
7(a)	Combination prescription (based on drugs yielding partial response) or 7(b) GO TO ECT																						
	All doses are TOTAL daily dose in milligrams (mg) and where necessary should be divided as indicated. Decision points denoted by orange and red shading.																						
	Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

b.i.d.: Twice daily.

[a]Divide quetiapine daily dose into two equal doses, except in "frail" regimen at 12.5 mg/day and 37.5 mg/day. At 12.5 mg/day give in evening only, at 37.5 mg/day split as 12.5 mg/25 mg.

[b]Divide gabapentin daily dose into two equal doses, except at 900 mg/day split as 400 mg/500 mg, and at 1500 mg/day split as 700 mg/800 mg.

[c]In patients with renal impairment gabapentin doses should be reduced according to renal function.

[d]In patients with hepatic or renal impairment, those using antihypertensives or those who are frail, titration should procede more slowly.

Table 4. Extensions.

Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
Risperidone	1.5	1.5	1.5	1.5	1.5	1.5	1.5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Single evening dose																						
Risperidone (frail)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Single evening dose																						
Quetiapine	250	250	250	250	250	250	250	250	300	300	300	300	300	300	300	300	300	300	300	300	300	300
Divided doses (i.e. start at 125 mg b.i.d.)																						
Quetiapine (frail)	125	125	125	125	125	125	125	125	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Divided doses																						
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43

b.i.d.: Twice daily.

schedules or trial duration. However, until the present algorithm is evaluated rigorously we do not know whether it is associated with improved clinical outcomes over usual practice. We acknowledge further limitations of this paper. First, the medication algorithm was derived from a consensus of physician preferences based on the characteristics of candidate drugs as enumerated earlier. The appraisal of evidence did not involve formal systematic reviews but did require three of the authors of this manuscript (SD, AB, TR) to undertake an evaluation of existing literature on drug efficacy and tolerability and to synthesize these findings with the views of the larger physician group in terms of acceptability/applicability and ease of use. Second, the present algorithm was designed specifically for a specialist geriatric psychiatry inpatient setting and we anticipate that in other settings, such as long-term care homes, some changes to the recommended drug sequence may be indicated. Thirdly, we acknowledge that some patients or their carers may be unwilling to consent to receive antipsychotics, or indeed other specific recommended drugs. However, the algorithm has been designed to cater for this scenario by allowing any treatment or series of treatments to be skipped.

Finally, we acknowledge that no medication algorithm can be applicable to every patient. As the algorithm has been developed and applied, we have encountered situations where the prescribing psychiatrist has chosen to deviate from it (e.g. in terms of doses and duration of treatment) due to individual patient characteristics and/or observed response. While the physicians have been able to follow the algorithm's principles and dosing schedules in most cases, we recognize that physicians must retain the discretion to make decisions around drug prescription which they see as in the patient's best interest. Therefore, this document should be seen as an overarching guide to sequential drug treatment rather than a rigid schema.

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