



The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An update on management of behavioral and psychological symptoms in dementia

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ABSTRACT

Geriatric patients with dementia frequently present with agitation, aggression, psychosis, and other behavioral and psychological symptoms of dementia (BPSD). We present an update of our previously published algorithms for the use of psychopharmacologic agents in these patients taking into account more recent studies and findings in meta-analyses, reviews, and other published algorithms. We propose three algorithms: BPSD in an emergent, urgent, and non-urgent setting. In the emergent setting when intramuscular (IM) administration is necessary, the first-line recommendation is for olanzapine (since IM aripiprazole, previously favored, is no longer available) and haloperidol injection is the second choice, followed by possible consideration of an IM benzodiazepine. In the urgent setting, the first line would be oral second-generation antipsychotics (SGAs) aripiprazole and risperidone. Perhaps next could be then prazosin, and lastly electroconvulsive therapy is a consideration. There are risks associated with these agents, and adverse effects can be severe. Dosing strategies, discontinuation considerations, and side effects are discussed. In the non-emergent setting, medications are proposed for use in the following order: trazodone, donepezil and memantine, antidepressants such as escitalopram and sertraline, SGAs, prazosin, and carbamazepine. Other options with less support but potential future promise are discussed.

Introduction

Dementia is estimated to affect over 5 million adults over the age of 65 in the United States— 1.6% of the population— and this percentage is projected to double to 3.3% by 2060 (Matthews et al., 2019). Dementia presents with cognitive impairment and memory loss, but it is usually the behavioral and psychological symptoms associated with dementia (BPSD) that have the greatest impact on both the quality of life of the patients and their caregivers. BPSD may be responsible for a third of costs related to dementia care (Schneider Beeri et al., 2002). BPSD has a broad definition that encompasses a diverse range of symptoms and behaviors including screaming, calling out, verbal and physical aggression, agitation, apathy, sexual disinhibition, defiance, wandering, hostility, intrusiveness, repetitive behavior and/or vocalization, hoarding, nocturnal restlessness, emotional lability, paranoid behaviors, and psychosis (hallucinations and/or delusions) (Ballard and Waite, 2006;

Osser and Fischer, 2013; Woodward, 2005). BPSD's most common symptoms are aggression, agitation, psychosis and mood symptoms (Byrne, 2005; Lyketsos et al., 2000).

The management of BPSD is challenging and many treatment modalities have been studied. Comprehensive overviews and guidelines are available (Bessey and Walaszek, 2019; Osser and Fischer, 2013). In this review, we update a 2013 algorithm (co-authored by two of the present authors, DNO and EM) focused on the role and use of psychopharmacological agents for treating these symptoms (Metzger et al., 2013; Osser and Fischer, 2013), taking into account new studies and reviews, and opinions expressed in other psychopharmacology guidelines and algorithms published in the last 7 years (Davies et al., 2018; Kales et al., 2015; Kales et al., 2019; Reus et al., 2016). Notably, the US Food and Drug Administration still has not approved any medications for this indication. We expanded on the previous proposal of two algorithms (as originally suggested by Rajesh Tampi, M.D) to three: one for patients

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with “emergent” BPSD needing immediate help with their agitation, one for “urgent” cases where agitation needs to be treated but there is space to wait a few days up to a few weeks for improvement, and one for “non-emergent” cases whose symptoms may be only moderately disruptive or who previously experienced more severe and emergent symptoms at some point, but are not at the point of care exhibiting them.

Methods

The methods used in developing new and revised algorithm of the Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) have been described in recent publications (Abejuela and Osser, 2016; Beaulieu et al., 2019; Giakoumatos and Osser, 2019; Wang and Osser, 2020). In brief, the authors reviewed the 2013 BPSD algorithm and conducted a systematic review of the literature on PubMed using Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015). We used as keywords available psychopharmacological agents for this (potential) indication including new randomized controlled trials (RCTs), recent guidelines, reviews, and meta-analyses. The search produced 231 articles from the period Jan. 1, 2018 to Aug. 10, 2020 (see Figure 1). This included articles from the 2013 algorithms and citations in the most recent reviews and guidelines. The authors considered short and long-term efficacy, effectiveness, tolerability, and safety of the different medication options, and then formulated an opinion-based qualitative distillation of this literature, focused on what changes seemed appropriate to make to the 2013 algorithms.

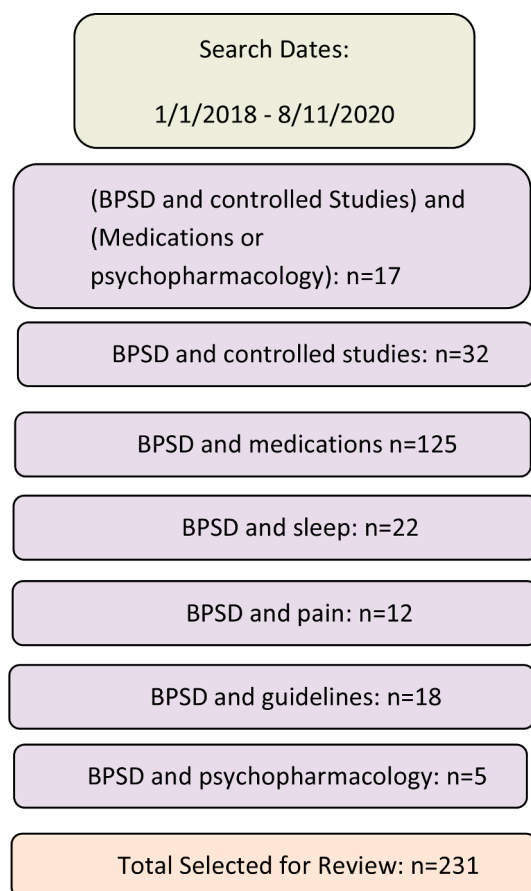


Figure 1. Prisma diagram of PubMed search outcomes for key word clusters used

Results

Flowcharts of the algorithms

Overviews of the algorithms appear in Figures 2, 3, and 4. Each “node” represents a clinical scenario where a treatment choice must be made, starting with initial treatments and progressing to suggestions for treatment-resistant cases. The evidence and reasoning supporting the recommendations at each node will be described below. Non-pharmacological treatments should always be considered first and were discussed extensively in our 2013 monograph (Osser and Fischer, 2013). In this update, we focus only on pharmacological treatments. The non-pharmacological approaches available are many and varied, including psychoeducational, sensory, sleep hygiene, and light therapy interventions, all of which also depend upon the setting (Bessey and Walaszek, 2019). The evidence supporting non-pharmacological techniques is variable, and beyond the scope of this paper. However, non-pharmacologic approaches are generally effective in the treatment of BPSD (Brodaty and Arasaratnam, 2012), unlikely to result in side effects (Scales et al., 2018) (Osser and Fischer, 2013; Scales et al., 2018; Zimmerman et al., 2018), and may even reveal underlying factors contributing to BPSD behaviors. This algorithm is not intended to replace these non-pharmacological approaches but instead they should be continued concurrently with appropriate pharmacologic treatments.”

Diagnosis of BPSD

When faced with a patient suspected of having BPSD, one must first consider the differential diagnosis since it is a diagnosis of exclusion. Delirium secondary to medical causes must be ruled out and treated (Osser and Fischer, 2013). Various approaches have been proposed for the clinical evaluations of BPSD, including “Describe, investigate, create, and evaluate” (DICE) (Kales et al., 2015) and several validated clinical scoring systems are available, including the Behavioral Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD) and the Neuropsychiatric Inventory (NPI) (Tible et al., 2017). Each of these engages caregivers to characterize the behavioral symptoms and to address potential modifiable factors in the patient’s medications, comorbid medical diagnoses, and environment. BPSD acuity can fluctuate, and the patient may switch from needing the non-urgent to the emergent algorithm. When differentiating emergent versus urgent versus non-emergent a general rule of thumb is that if the clinician, patient, or others are in imminent danger due to behaviors related to BPSD, consider the emergent algorithm. Examples of this include aggression towards self or others (for example, pulling out intravenous lines). If the patient was recently aggressive but now presents as calmer, the situation may still be considered emergent if the patient is thought to be at high risk to re-escalate quickly. A non-emergent situation would be one where the patient does not appear to be at imminent risk of putting him/herself or others (Osser and Fischer, 2013). An urgent situation is where patient is in distress, but there is space for a few days to weeks for improvement.

In the following algorithm flowcharts and descriptions, we have proposed our order of preferences based on examination of the cited studies and meta-analyses weighing qualitatively the benefits and harms of the options. These recommendations are not to be followed rigidly, but rather prescriber and patient preferences (especially when backed by specific reasoning pertinent to the particular situation) can justify deviating from the proposed recommended sequences.

Emergent Algorithm

Important Note: In this algorithm for the Emergent situation and the subsequent algorithms for Urgent and Non-Urgent patients, antipsychotics are recommended at different points. Prescribers should be aware, however, that none of these agents has been approved by the FDA

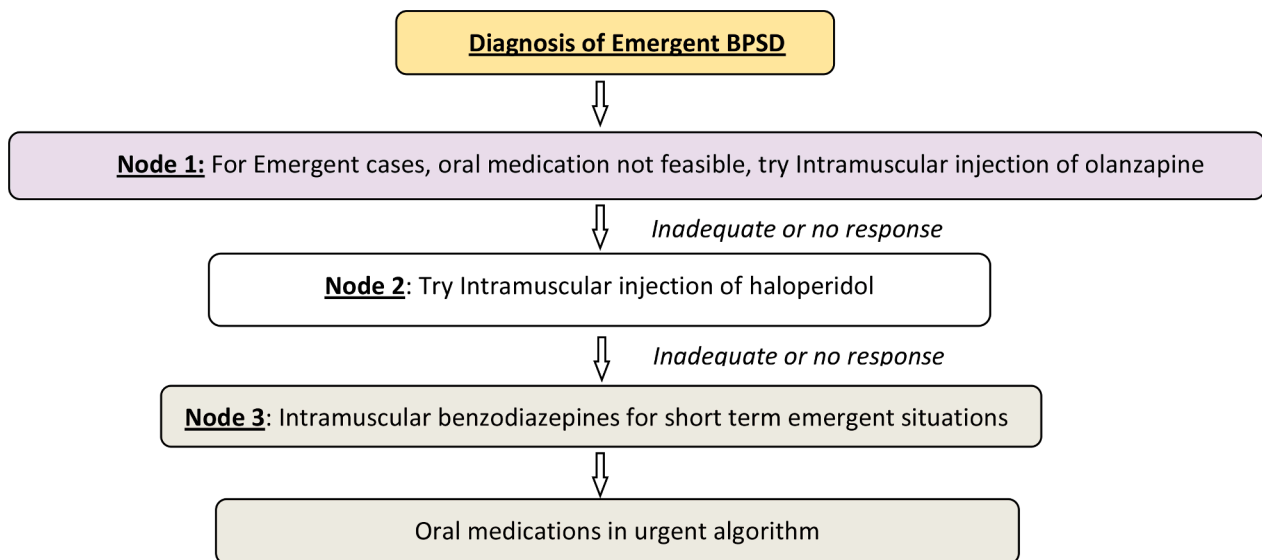


Figure 2. Flowchart for Emergent BPSD Management

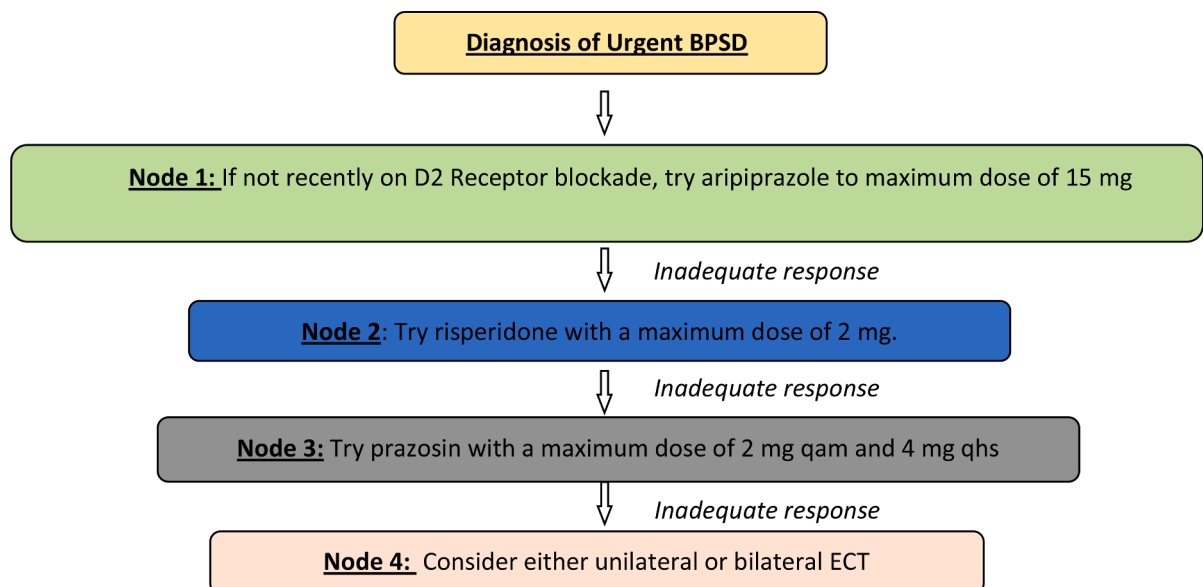


Figure 3. Flowchart for Urgent BPSD Management

for any BPSD symptoms, and they have specifically been deemed ineffective for dementia-related psychosis (FDA, 2008). Though some efficacy has been found for some BPSD symptoms in meta-analyses, there are significant adverse effects including an increased risk of death over 10-12 week periods of oral use compared with placebo (Schneider et al., 2005). The package insert warning for this class of medications lists the risk of death to be 3.5% versus 1.5% on placebo. This would be a Number Needed to Harm of 50 for the outcome of death. Also, the risks of strokes and transient ischemic attacks are significantly higher with use of this class of medication compared with placebo. No difference has been found in these risks among the different drugs in this class (Schneider et al., 2005). These risks should be taken into consideration and discussed with the patient and family before prescribing

Node 1. Intramuscular Injection of Olanzapine.

After diagnosis of BPSD and classification as an emergent situation, if oral medication is not an option, we recommend considering first the second generation antipsychotic (SGA) olanzapine in its intramuscular (IM) formulation, specifically 1.25 mg to 5 mg, up to every 30-60

minutes using up to three doses per day (Osser and Fischer, 2013). In the previous algorithm, we thought IM aripiprazole was preferable (Osser and Fischer, 2013). However, this product is no longer manufactured (and no generic company is providing it) apparently due to low demand. Olanzapine's shortcomings with respect to metabolic and anticholinergic side effects (Chen et al., 2020) previously made it a second choice, though it was effective. Olanzapine also carries an increased risk of cerebral vascular adverse events compared to other antipsychotics (Yunusa et al., 2019). Duong and colleagues' retrospective chart review of 85 inpatient BPSD encounters found a favorable response with IM olanzapine in 63% of the patients, though there was a 41% frequency of adverse events such as significant somnolence and cardiovascular instability (Duong et al., 2015).

Ziprasidone is another IM option that we did not consider in 2013. In RCTs of IM medications for agitation in patients with diverse psychiatric problems seen in emergency room settings (mostly schizophrenia and mania, as well as some organic syndromes), ziprasidone performed less well than olanzapine or haloperidol (Klein et al., 2018; Mantovani et al.,

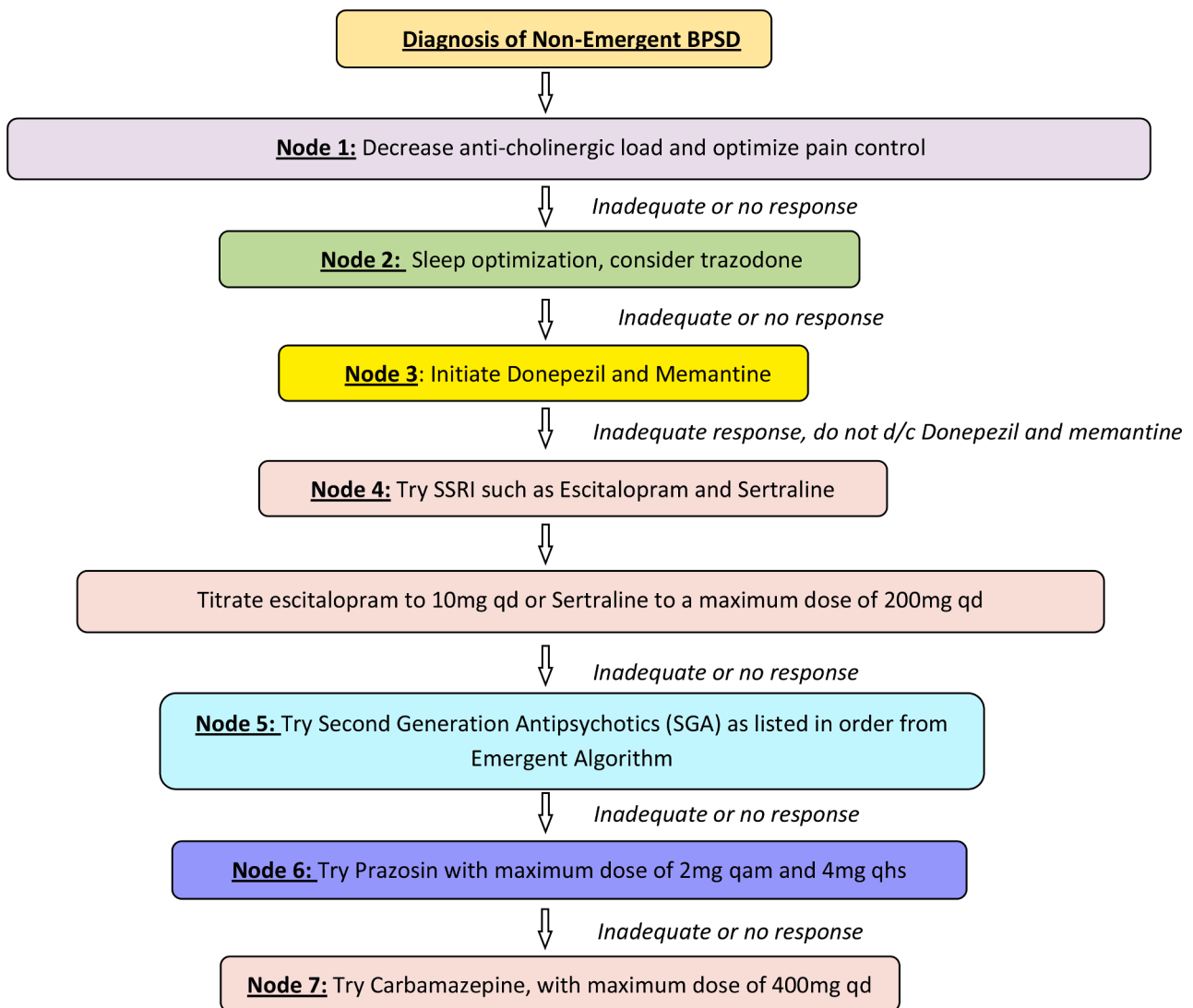


Figure 4. Flowchart for Non-Emergent BPSD

2013) and there are safety concerns regarding QTc prolongation. Hence, we do not favor it for this indication.

Node 2. Intramuscular Injection of Haloperidol

IM haloperidol is often used, though we did not include it in our recommendations in the previous algorithm. There are no robust studies available for validating or disqualifying the use of IM haloperidol, particularly in the setting of emergent BPSD, but in the two studies of emergency room treatment of agitation just cited, haloperidol was comparable in effectiveness to IM olanzapine. In one of the trials, IM olanzapine 10 mg was of comparable efficacy to IM haloperidol 2.5 mg combined with IM midazolam 7.5 mg, and produced fewer significant side effects: the odds ratio for side effects being higher (1.6) with the olanzapine compared with the combination (Mantovani et al., 2013). However, a recent large observational study found that the risk of death when benzodiazepines are combined with antipsychotics during oral treatment of dementia patients was 2.19 with prolonged use of the benzodiazepine over 180 days (Nørgaard et al., 2020). Oral haloperidol (without a benzodiazepine) is also hazardous over the long term in this population (Reus et al., 2016). Nevertheless, for the emergent situation, the risks of haloperidol with or without a benzodiazepine may be acceptable if IM olanzapine has failed. It should be noted that chronic use of haloperidol for non-emergent BPSD management is not recommended; compared to other antipsychotics: haloperidol use is associated with a 50-100% increase in mortality (Osser and Fischer, 2013; Reus

et al., 2016).

Node 3. Intramuscular use of Benzodiazepines

Generally, benzodiazepines should be avoided in this population. They are associated with falls, impaired cognition, and BPSD exacerbations (Gerlach and Kales, 2018; Mathys, 2018). Our rationale for proposing the possible use of benzodiazepines IM here is that in the case of true emergencies where immediate sedation is essential and olanzapine and haloperidol have failed, there may be a role for these agents. Both Gerlach and colleagues and Davies and colleagues suggest using benzodiazepine as needed for extreme BPSD presentations (Davies et al., 2018; Gerlach and Kales, 2018) involving agitation. Special circumstances such as patients with Parkinson's disease, Lewy Body Dementia, or recent neuroleptic malignant syndrome, or patients about to undergo a necessary medical procedure may also be indications for IM benzodiazepine, but one must be mindful of possible rebound effects and falls (Davies et al., 2018). We recommend lorazepam 0.5 mg IM at four hour intervals with maximum dose of 2 mg. Note that studies have linked benzodiazepine use to worsening of cognition (McDermott and Grue-newald, 2019). In the previous version of this algorithm, we advocated avoidance of benzodiazepines under all circumstances, but in this update we only recommend it third-line for truly emergent situations and short-term special circumstances. If the patient recently consumed alcohol and received olanzapine, there is a risk of respiratory depression with giving benzodiazepines so great caution is necessary in this

circumstance (Wilson et al., 2012).

Urgent Algorithm

Node 1. Aripiprazole

If IM medication can be avoided, we recommend aripiprazole as the first-line oral medication for emergent BPSD. The use of aripiprazole is supported by a systematic review (Jin and Liu, 2019) and a meta-analysis of 17 studies that concluded aripiprazole may provide an optimal combination of safety and efficacy for BPSD treatment (Yunusa et al., 2019). In the meta-analysis, aripiprazole outperformed placebo for BPSD on the Cohen-Mansfield Inventory (CMAI), Brief Psychiatric Rating Scale (BPRS), and NPI (Yunusa et al., 2019). Among SGAs, aripiprazole had the best improvement in NPI scores (Yunusa et al., 2019). In the systematic review, aripiprazole was superior to placebo (Jin and Liu, 2019). However, the American Psychiatric Association guidelines for the use of antipsychotics in BPSD (Reus et al., 2016) found only a modest effect size for aripiprazole on agitation (SMD of 0.31), similar to risperidone (0.37). However, side effects appeared milder, particularly fatigue and extrapyramidal symptoms. They concluded that aripiprazole or risperidone were reasonable when BPSD was “severe, dangerous, and /or caused significant distress” after having a suitable discussion of medication benefits and risks (Reus et al., 2016). Dosage would start at 2-2.5 mg of aripiprazole daily (Davies et al., 2018; Mathys, 2018). Target dose should be 5 mg at the end of 2 weeks, increasing by 5 mg every 2 weeks as clinically indicated (Mathys, 2018). We recommend a maximum dose of 15 mg, consistent with Mathys and colleagues’ recommendation (Mathys, 2018). There is a theoretical risk that due to its partial dopamine agonist properties, aripiprazole could have an activating effect. Based on case studies, it is hypothesized that initiation of aripiprazole after previous use of dopamine blocking agents may activate upregulated dopamine receptors and exacerbate agitation (Chaumette et al., 2018). Clinicians should be alert to this possibility. Nevertheless, given its superior safety profile, and adequate evidence of efficacy, we recommend it as the first oral medication treatment option for emergent BPSD symptoms.

Node 2. Risperidone

Risperidone is approved for BPSD treatment in Australia (Kalisch Ellett et al., 2019) and the United Kingdom, and is also approved for aggression and psychotic symptoms in Alzheimer’s in Canada. In addition to the systematic review (Jin and Liu, 2019) and meta-analysis (Yunusa et al., 2019) cited earlier, results from 6 RCTs were positive in 4 (one minimally so) (Reus et al., 2016). As noted above, the overall size of the effect was small and generally barely statistically significant but did reach a standardized mean difference (SMD) of 0.46 on overall symptoms (Reus et al., 2016). We therefore recommend risperidone as the next oral medication to try.

We recommend an initial dose of 0.25 mg to 0.5 mg on the first day (Davies et al., 2018; Mathys, 2018; McDermott and Gruenewald, 2019), increasing slowly by 0.25 mg per day as needed to a maximum dose of 2 mg per day (Davies et al., 2018; Mathys, 2018). Some studies suggest an adequate trial time for risperidone is approximately 3 weeks (Davies et al., 2018; Osser and Fischer, 2013). However, it appears partial improvements can be observed as early as 1 week (Suh et al., 2006). Risperidone is relatively tolerable; it is less sedating, and thus less likely to lead to falls and fractures than some other SGAs (Yunusa et al., 2019). Risperidone should be avoided in patients with Parkinson’s and Lewy Body Dementia (LBD) due to its dopamine blockade properties leading to its association with more severe extrapyramidal side effects in these kinds of dementia (Yunusa et al., 2019). A better option for patients with LBD and Parkinson’s Dementia presenting with BPSD could be clozapine (Drach, 2011). Quetiapine has been considered theoretically useful and is often employed by clinicians (Maust et al., 2020), even though it has no apparent efficacy in Alzheimer’s dementia BPSD symptoms, and the evidence of usefulness in LBD is weak at best (Reus et al., 2016).

Risperidone has been associated with increased morbidity and mortality in patients with severely compromised cardiovascular health (Jin and Liu, 2019; Reus et al., 2016; Yunusa et al., 2019). In Yunusa and colleagues’ network meta-analysis, among SGAs, risperidone had the most improved CMAI score, but was not as efficacious or safe overall as aripiprazole (Yunusa et al., 2019). In Teranishi and colleagues’ 8-week randomized trial of 82 patients, 27 received risperidone and one experienced sudden death likely related to cardiac infarct (Teranishi et al., 2013). Risperidone should be avoided in patients with vascular dementia (Reus et al., 2016; Yunusa et al., 2019). Patients responding to risperidone should probably be maintained on it for several months at least. Devanand and colleagues found 60% of Alzheimer’s patients who received and had positive results from risperidone for 16 weeks experienced relapse of symptoms after discontinuing risperidone, while only 33% relapsed if maintained on risperidone (Devanand et al., 2012).

Node 3. Prazosin

Generally speaking, the options to consider after antipsychotics in the Urgent Algorithm have not received a large amount of study. Among these options, we speculate that prazosin might be selected. An adrenalin-mediated treatment would offer a different mechanism of action against the agitated behaviors, and there is extensive experience in the treatment of post-traumatic stress disorder suggesting a role in controlling symptoms deriving (at least in part) from such mechanisms

Prazosin is supported by 2 clinical trials—Wang and colleagues 2009 (Wang et al., 2009) and Peskind and colleagues 2015 (Peskind, 2015). In the 2009 study, 1 mg at bedtime was the starting dose and it was increased by 1-2 mg every 3-7 days up to a maximum of 2 mg qAM and 4 mg qHS (Wang et al., 2009). The duration of treatment was 8 weeks. Prazosin was effective for behavioral agitation management based on the BPRS, NPI, and subjective Clinical Global Impression (CGI) changes (Wang et al., 2009). The NPI was reduced by 19 points with prazosin, 2 points with placebo, and active drug side effects were similar to placebo. The 2015 study suggested that 4 mg twice a day for 12 weeks was effective based on BPRS, NPI, and CGI (Peskind, 2015). These positive changes were observable within the first week of treatment (Wang et al., 2009), and for this reason we include prazosin toward the end of the options for emergent BPSD cases despite the small evidence-base.

Node 4. Electroconvulsive Therapy (ECT)

At this point, if all medications (antipsychotics IM, antipsychotics orally, prazosin, even benzodiazepines) have failed, electroconvulsive therapy (ECT) should be considered. Evidence for ECT comes from case series demonstrating effectiveness and relative safety in patients with dementia and BPSD (Davies et al., 2018). In Ujkaj and colleagues’ retrospective report, 16 patients with an average age of 66 underwent bilateral ECT treatments with improvement, and the main concern was post-ECT confusion that largely dissipated by 2 days (Ujkaj et al., 2012). A more recent retrospective study of 60 patients treated with ultra-brief right unilateral pulses of ECT found a decrease in the Pittsburgh Agitation Scale and suggested ECT can be effective after only 3 sessions and is sustained through the 6th ECT treatment session (Hermida et al., 2020). A review by van den Berg and colleagues suggests that though ECT may be effective within a few sessions, relapse is not uncommon after ECT cessation (van den Berg et al., 2018). In sum, the current literature does not provide clear guidance on the optimal number of treatments, but it seems reasonable that if the positive effects are not seen within 3 sessions of right unilateral ultra-brief pulse ECT, then transition to bilateral ECT or halting ECT should be considered. If positive results are seen, ECT should be continued until improvement plateaus, after which discussion with family about treatment options (discontinuation versus maintenance) should occur.

Non-Emergent Algorithm

Node 1. Decrease Anti-cholinergic Load and Optimize Pain Control

It is well established that the cholinergic system becomes deficient with age, resulting in high vulnerability in the geriatric population to medications with anticholinergic properties. In Carriere and colleagues' study of 6912 participants who were 65 years and above, it was clear that anticholinergics produced worsening of cognition and dementia, and if the anticholinergic agents were stopped the negative impacts were decreased (Carriere et al., 2009).

Uncontrolled pain is a potent contributor to BPSD (Sampson et al., 2015; Tampi et al., 2017). Pain is common in those with dementia, and the sources can be many. Studies suggest over a period of 5 years, 85% of patients with dementia will experience substantial pain (Sampson et al., 2015). Thus, it is very important to examine if pain is adequately controlled. The American Geriatric Society (AGS) recommends acetaminophen up to maximum dose of 3 grams, then oral morphine up to 20 mg, then buprenorphine transdermal patches up to 10 micrograms per hour, then pregabalin up to 300 mg daily (Tampi et al., 2017). This guideline developed by AGS has been proven to be effective in multiple studies (Tampi et al., 2017).

Node 2. Sleep Optimization, Consider Trazodone

It is also important to optimize patients' sleep quality, as poor sleep in general is common, and is associated with poor cognition, attention, and development of BPSD symptoms (Kabeshita et al., 2017). Trazodone is known for its sedating properties and has been utilized for BPSD symptom management for more than two decades (Davies et al., 2018; Henry et al., 2011). Trazodone is largely a histaminergic antagonist with some cholinergic agonist activity (Davies et al., 2018), and recommended doses for BPSD management are 12.5-25 mg at bedtime (Gerlach and Kales, 2018). When trazodone is compared to haloperidol, it has been shown to be at least as efficacious for BPSD agitation treatment (Sultzer et al., 1997; Teri et al., 2000). Results suggest trazodone is more efficacious than haloperidol in the presence of mood symptoms (Sultzer et al., 2001) while having a more tolerable side effect profile than haloperidol (Sultzer et al., 1997; Sultzer et al., 2001). When trazodone was compared to placebo in a 12 week study consisting of 31 fronto-temporal dementia patients, trazodone improved BPSD symptoms more (Lebert et al., 2004). These studies suggest that trazodone may not only improve sleep but may have an independent positive effect on BPSD symptoms. However, trazodone fall risk is similar to that of benzodiazepines, and this risk should be carefully evaluated and the medication avoided in high-risk individuals (Bronskill et al., 2018).

Node 3. Donepezil and Memantine

Though the evidence for donepezil (and other cholinesterase inhibitors) and memantine for the acute treatment of BPSD is very limited, they are useful in other ways in these patients and may have secondary benefit for BPSD (Reus et al., 2016).

Donepezil and memantine should be initiated (McDermott and Gruenewald, 2019) if the patient is not already on them. Though the actual benefits for BPSD symptom control are small, both are FDA-approved for the cognitive impairment of Alzheimer's dementia. Furthermore, cholinesterase inhibitors have been shown to be able to delay BPSD onset (McDermott and Gruenewald, 2019). Both medications can be started in close succession and with possible synergistic benefit (McDermott and Gruenewald, 2019). Donepezil is considered safe and well tolerated until the neuro-cognitive disorder becomes terminal (McDermott and Gruenewald, 2019). Evidence for the use of donepezil extends to Parkinson's disease and LBD as well (Gerlach and Kales, 2018). Administration of donepezil and memantine should be ongoing unless they seem to be exacerbating BPSD symptoms (Davies et al., 2018).

Node 4. Selective Serotonin Reuptake Inhibitors (SSRIs) such as Escitalopram and Sertraline

After considering donepezil and memantine, we recommend trying SSRIs such as escitalopram and sertraline, especially if depression may be contributing to the presentation (McDermott and Gruenewald, 2019). Studies to date have used racemic citalopram, of which escitalopram is an enantiomer. From 1997, 2002, and 2007, three trials from Pollock and colleagues (Pollock et al., 2007; Pollock et al., 2002; Pollock et al., 1997) demonstrated the effectiveness of citalopram. More recently, the CitAD trial found that 30 mg per day of citalopram improved BPSD symptoms in non-depressed outpatients with Alzheimer's dementia (Porsteinsson et al., 2014). Citalopram arguably now should be avoided because of what we know today about its effects to prolong the QTc interval (Vieweg et al., 2012). There are, however, two studies calling into question this risk: Zivin and colleagues and Ray and colleagues studied two large population cohorts and could not find an increased risk of ventricular arrhythmia, sudden cardiac death, or other mortality (Ray et al., 2017; Zivin et al., 2013). However, these studies are only somewhat reassuring because controlled studies clearly show that citalopram does increase QTc much more than escitalopram and other SSRIs (Vieweg et al., 2012). The FDA decreased the recommended maximum dose of citalopram to 20 mg per day for those 65 years and above (FDA, 2017). Escitalopram likely increases QTc about 3.5-7 ms and in a dose-related pattern (Beach et al., 2014; Thase et al., 2013), but does it less so than citalopram, and does not carry an FDA warning. Due to this significant cardiac risk concern and the nature of medical vulnerability in the population, it seems safer to recommend escitalopram over citalopram.

Nine weeks are required for full response with citalopram (Davies et al., 2018; Weintraub et al., 2015), and it seems reasonable to expect the same timeline for escitalopram. We recommend a starting dose of 10 mg (Mathys, 2018). Alternatively, sertraline does not pose significant QTc concerns. A Cochrane review in 2011 concluded that sertraline was efficacious for BPSD's agitation symptoms (Seitz et al., 2011). Sertraline is generally well-tolerated in this patient population (Finkel et al., 2004; Lancôt et al., 2002; Lyketsos et al., 2003; Magai et al., 2000), and women may respond better than men (Lyketsos et al., 2003). Despite some conflicting evidence, given the positive Cochrane review (Seitz et al., 2011) and sertraline's relatively acceptable side effect profile, we find it a suitable alternative to escitalopram. Also, though antipsychotics may not have the same response latency as SSRIs, sertraline is likely better tolerated than antipsychotics (Mathys, 2018) especially with long term use. When sertraline is combined with anti-psychotics for BPSD, the hazard ratio for death was actually improved at 0.61 in a new large observational study (Nørgaard et al., 2020). Other SSRIs are less well-studied and thus not included in this algorithm. Fluoxetine and paroxetine are P450 2D6 inhibitors which could result in troublesome drug-drug interactions (Mathys, 2018). SSRI-induced syndrome of inappropriate antidiuretic hormone is more common in older patients and can lead to dangerously low serum sodium (Covyeou and Jackson, 2007; Kirby et al., 2002). We recommend checking sodium 2 weeks after SSRI initiation and any dose increase, and periodic checks thereafter.

Node 5. Second Generation Antipsychotics

If BPSD symptoms remain uncontrolled, consider resuming the last SGA that worked for the patient or follow the oral SGA medication recommendations in the emergent algorithm. Because SGA use in this population carries a small but significant risk of sudden death and strokes, it is important to have a candid conversation with patient and family about the risks associated with these medications in the context of long term non-emergent use (Reus et al., 2016).

Node 6. Prazosin

Considering that clinical trials on prazosin involved patients with Alzheimer's with non-emergent BPSD symptoms, and that positive results were seen as quickly as 1 week, prazosin is certainly worth

considering here, as discussed in the emergent algorithm (Wang et al., 2009). The dose and duration of treatment were reviewed above.

Node 7. Carbamazepine

After an adequate trial of prazosin, we cautiously recommend carbamazepine. This medication has significant side effects, including drug interactions, liver toxicity, agranulocytosis, and hyponatremia. Carbamazepine use thus requires hepatic enzyme monitoring, white count monitoring in this population (McDermott and Gruenewald, 2019), and electrolyte monitoring. If the reader is at this node of the algorithm, the patient has likely suffered with BPSD symptoms for a significant amount of time, so carbamazepine may warrant a trial despite these concerns, as it is supported by 2 small studies with positive results (Gerlach and Kales, 2018). Recommended starting dose is 100 mg daily. If the patient is particularly frail, consider starting at 50 mg (Davies et al., 2018), titrating up to 200 mg per day on day 4, then to 300 mg on day 8, to a maximum dose of 400 mg daily (Davies et al., 2018).

Medications to Usually Avoid in BPSD Management

With exceptions in certain clinical situations described previously, we recommend avoiding the following medications: valproic acid, olanzapine, quetiapine, and benzodiazepines. In a 24 month multi-site randomized controlled trial, valproic acid was shown to be not only ineffective, but also to cause significant drowsiness, increased rates of falls, and loose stools (McDermott and Gruenewald, 2019). Other experts have concluded that any possible benefit of valproate in BPSD is outweighed by these adverse effects (Davies et al., 2018; Gerlach and Kales, 2018; McDermott and Gruenewald, 2019).

Olanzapine is best avoided for other than very short term use in BPSD due to its metabolic properties and anticholinergic effects (Chen et al., 2020; Davies et al., 2018). In a 12 month retrospective cohort study of 133 patients with Alzheimer's dementia, Jenraumjit and colleagues demonstrated that anticholinergic effects on cognition were worse than the cognitive impairment caused by benzodiazepines (Jenraumjit et al., 2020). The metabolic side effects of olanzapine are the most severe of any of the antipsychotics (Chen et al., 2020). A single dose of olanzapine causes significant insulin resistance, impairment of lipid metabolism, and adverse effects on inflammatory markers (Hahn et al., 2013), though these metabolic effects may be less severe in the elderly (Rothschild et al., 2008). Regarding efficacy, meta-analysis of three trials showed oral olanzapine to be without benefit for BPSD treatment (Reus et al., 2016). In addition, olanzapine increases cardiovascular disease risk (Jin and Liu, 2019; Yunusa et al., 2019). We believe the risks of using olanzapine outweigh any possible benefits in the non-emergent algorithm.

Quetiapine, though commonly used by clinicians, has not been found to be more efficacious than placebo for any symptoms of BPSD in three studies (two from nursing homes, one involving non-nursing-home subjects) (Reus et al., 2016). In a fourth study (locale of patients not stated) there was a benefit on the Clinical Global Impression scale, but confidence was reduced by there being no dose-response relationship (Reus et al., 2016). Standardized mean differences of benefits compared with placebo on different symptoms ranged from 0.03 to 0.16. Clinicians may be choosing quetiapine because of fewer extrapyramidal side effects than other SGAs (Maglione et al., 2011; Maust et al., 2015) However, this should not normally outweigh the consistent evidence of insignificant benefits in large controlled studies.

Benzodiazepines may exacerbate cognitive impairment and are also associated with increased rates of falls as noted earlier. Their use should be limited to infrequent circumstances as described in the emergent algorithm.

Medications Worthy of Mention and Requiring Further Study: Tetrahydrocannabinol (THC) and its Analogues, Pimavanserin, and Gabapentin

Shelef and colleagues administered 2.5 mg of THC to 11 patients and found improved symptoms related to dementia (Shelef et al., 2016). Woodward and colleagues' retrospective study of 40 patients on dronabinol showed improvement in BPSD symptoms (Woodward et al., 2014), and a case report of two patients taking nabilone found improved BPSD symptoms (Passmore, 2008). Nabilone was superior to placebo on the CMAI and Mini Mental State Examination results, but the Severe Impairment Battery score favored placebo (Herrmann et al., 2019). Several studies suggest the use of cannabinoids is relatively safe (Timler et al., 2020), and van den Elsen found no increased rates of falls in 18 patients on oral THC (van den Elsen et al., 2017). Given the popularity of THC, providers likely will encounter questions pertaining to this, but current evidence is limited.

Pimavanserin, an antipsychotic FDA-approved for psychosis in Parkinson's Disease, is being actively studied in BPSD. A phase 2 study favored pimavanserin over placebo for agitation control in patients with Alzheimer's (Cummings et al., 2018). Kales and colleagues' consensus statement also listed pimavanserin as a potential treatment for psychotic symptoms of BPSD (Kales et al., 2019) and the FDA is considering it for this indication. Pimavanserin also is an agent of interest for treatment of psychosis in Lewy Body Dementia and Parkinson's Disease Dementia (Cummings et al., 2014; Hershey and Coleman-Jackson, 2019).

Gabapentin has the potential to be particularly helpful if the BPSD symptoms are in the context of neuropathic pain. Evidence for its use is supported by 14 case reports that showed positive effects (Supasitthumrong et al., 2019). However, this medication needs dose-finding randomized controlled trials as there appears to be a wide range of effective dosages in the current literature (200 - 3600 mg total daily dose (Supasitthumrong et al., 2019)). Results on agitation in patients with LBD are more limited (Supasitthumrong et al., 2019). Though results for gabapentin are promising, these are only case reports.

Concluding Comment

The use of psychopharmacology for BPSD will remain a challenge, despite this effort to collate and distill the evidence base available as of August, 2020. Equipped with an imperfect pharmacopeia for BPSD management, the prescribing clinician should consider the algorithms presented here taking into consideration each patient's individual characteristics. For example, the approach to a 70-year-old 200 pound male with Alzheimer's disease who is combative with caregivers will quite likely be different from the approach to a 90-year-old non-ambulatory 100 pound female with Parkinson's disease and similar behaviors. Success with these medications also depends on good communications. Those making medical decisions on behalf of patients should be allowed an opportunity to communicate what a patient's priorities would be, and should be helped to put in perspective the various risks and possible benefits. Current practice guidelines advise that antipsychotic medication trials should not exceed 4 weeks, and if the medication is effective, attempts to taper the medication should be tried by 4 months of initiation unless the patient has previously failed medication tapering (Reus et al., 2016). Practitioners will need to remain alert to new studies and changes in guideline recommendations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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