International Psychogeriatrics (2024), 36:4, 251–262
doi:10.1017/S1041610222001030X

REVIEW

Reduction and prevention of agitation in persons with neurocognitive disorders: an international psychogeriatric association consensus algorithm

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ABSTRACT

Objectives To develop an agitation reduction and prevention algorithm is intended to guide implementation of the definition of agitation developed by the International Psychogeriatric Association (IPA)

Design: Review of literature on treatment guidelines and recommended algorithms; algorithm development through reiterative integration of research information and expert opinion

Setting: IPA Agitation Workgroup

Participants: IPA panel of international experts on agitation

Intervention: Integration of available information into a comprehensive algorithm

Measurements: None

Results The IPA Agitation Work Group recommends the Investigate, Plan, and Act (IPA) approach to agitation reduction and prevention. A thorough investigation of the behavior is followed by planning and acting with an emphasis on shared decision-making; the success of the plan is evaluated and adjusted as needed. The process is repeated until agitation is reduced to an acceptable level and prevention of recurrence is optimized. Psychosocial interventions are part of every plan and are continued throughout the process. Pharmacologic interventions are organized into panels of choices for nocturnal/circadian agitation; mild-moderate agitation or agitation with prominent mood features; moderate-severe agitation; and severe agitation with threatened harm to the patient or others. Therapeutic alternatives are presented for each panel. The occurrence of agitation in a variety of venues—home, nursing home, emergency department, hospice—and adjustments to the therapeutic approach are presented.

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Conclusions The IPA definition of agitation is operationalized into an agitation management algorithm that emphasizes the integration of psychosocial and pharmacologic interventions, reiterative assessment of response to treatment, adjustment of therapeutic approaches to reflect the clinical situation, and shared decision-making.

Key words International Psychogeriatric Association (IPA), agitation, algorithm, psychosocial intervention, pharmacotherapy, shared decision-making, nocturnal agitation, antipsychotics, hospice, emergency department

Introduction

Fifty-five million people worldwide are currently living with Alzheimer's disease (AD) dementia or dementia of other types and that figure is projected to rise to 152 million by 2050 if ways of preventing or delaying the onset are not identified (Patterson, 2018). AD and dementia are accompanied by a wide variety of neuropsychiatric syndromes and the increasing number of persons with dementia patients globally forecasts a growing number with behavioral changes (Zhao *et al.*, 2016). Neuropsychiatric syndromes are among the most challenging features of dementia for patients and care partners (Delfino *et al.*, 2021) and ameliorating their impact will substantially improve the quality of life of patients and their care partners.

Agitation is one of the most common neuropsychiatric syndromes to occur in dementia. Agitation syndromes occur in all forms of dementia and may emerge at any point in the spectrum of severity (Zahodne *et al.*, 2015). Agitated behavior occurs in up to 70% of patients in the course of AD dementia and is more likely to occur in patients with more severe cognitive impairment.

In 2015, the International Psychogeriatric Association (IPA) published a definition of agitation in cognitive disorders (Cummings *et al.*, 2015a). The goal of the publication was to provide a uniform definition of agitation that could be applied in clinical and research settings including biological studies, epidemiological investigations, psycho-social intervention research, and clinical trials. The 2015 definition has been widely used in research and clinical trials. Sixty-five percent of agitation trials initiated since 2015 and using a specific definition of agitation for inclusion in the trial used the IPA criteria (Zhong *et al.*, 2021). The 2015 provisional definition has been reviewed, updated, and adjusted to allow its application in a wider range of venues in which agitation occurs in cognitively impaired individuals (Sano, 2022).

The IPA Agitation Workgroup responsible for the updated agitation definition developed an agitation assessment and treatment algorithm aimed at reducing or preventing the recurrence of agitation in individuals with cognitive impairment. The algorithm presents specific strategies to evaluate agitation, determine its possible causes, formulate psychosocial interventions, identify pharmacologic treatment if appropriate for the circumstances, assess the success of the interventions, and seek ways to prevent potentially recurrent agitation. We use "psychosocial intervention" to include therapies called "nonpharmacologic intervention" in some publications and "behavioral intervention" in others. The use of algorithms reduces practice variance, builds on available expertise, and may improve patient outcomes. Standardization of an approach to agitation may facilitate outcomes research and cost-effectiveness studies.

The IPA Agitation Workgroup assessment and treatment algorithm is presented here. The goal of the algorithm is to guide clinicians by providing knowledge and tools to respond to agitation in persons with cognitive impairment and describe best practices for agitation amelioration and prevention. Agitation can occur in many venues including the patient's home, nursing homes and residential settings, emergency departments (ED), and hospice. The definition of agitation encompasses behaviors that occur in all these venues; the algorithm for responding to agitation varies according to the circumstances in which the agitation occurs. Strategies for applying the algorithm in varying clinical circumstances are presented.

Methods

The IPA Agitation Workgroup is comprised of individuals with expertise in geriatric psychiatry, neuropsychiatry, neuropsychology, geropsychology, and nursing, and the algorithm is based in part on expert opinion. The literature concerning agitation management strategies was reviewed with comprehensive review of articles with key words including "management algorithm". A reiterative process of refining the algorithm and integrating the updated agitation definition was pursued through electronic communication and virtual meetings. Previous publications of algorithms and guidelines including the Psychopharmacology Algorithm Project at the Harvard South Shore Program (Chen *et al.*, 2021), the American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia (Reus *et al.*, 2016), and other evidence-based algorithms were

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

reviewed. Use of psychosocial interventions was examined and included in the process of developing the integrated psychosocial/pharmacologic algorithm (Abraha *et al.*, 2017). The alternative algorithms or guidelines reviewed differed in their perspective and construction from those developed by the IPA Agitation Workgroup and presented here. Most previous algorithms focused on pharmacologic management of agitation whereas the goal of the IPA Agitation Workgroup was to provide clinicians with both psychosocial and pharmacological strategies. The IPA Agitation Workgroup algorithm includes agitation prevention and risk reduction strategies as well as agitation amelioration approaches employing psychosocial, educational, and pharmacologic interventions. There is an emphasis on evaluation prior to any intervention and continuously thereafter. We present an overall strategy for Investigating agitation episodes, Planning interventions, and Acting to implement the plan (IPA). This approach applies to both psychosocial and pharmacologic interventions. We describe the psychosocial therapies and pharmacologic interventions applicable in different care venues, pharmacologic treatments specific to patient circumstances, and the integration of pharmacologic and psychosocial approaches.

Results

Investigate, Plan, and Act (IPA)

An individual's behavior is the result of the complex interactions between internal and external causes (Gerritsen *et al.*, 2019). In addition to the internal biological or psychological patient factors, there are external care partner and environmental influences associated with agitation. A thorough analysis of these factors is necessary to enable treatment in general and for the specific choice and use of psychosocial interventions. The Treatment Routes for Exploring Agitation (TREA) method guides an investigation approach that hypothesizes that agitation is the expression of an unmet need and structures inventions to fit the person's needs, history, preferences, and abilities (Cohen-Mansfield *et al.*, 2012). Investigation may lead to the identification of anxiety, apathy, boredom, or depression as important causes or contributors to agitation. In several countries, researchers and practitioners have developed care programs with an analysis-focused approach towards agitation, for instance Describe, Investigate, Create, and Evaluate (DICE) (Kales *et al.*, 2015) and the Targeted Interdisciplinary Model for Evaluation and Treatment of neuropsychiatric symptoms (TIME) (Lichtwarck *et al.*, 2016).

Programmatic care approaches for agitation are based on recommendations of international national guidelines (IPA, National Institute for Health and Care Excellence (NICE); UK], Verenso (Dutch), BMG [Bundesministerium für Gesundheit; German]) and emphasize the importance of a systematic approach to analyzing agitation from an interdisciplinary perspective. Accordingly, the programs adopt a reiterative approach to assessing, treating, and reassessing agitation. The process of assessing and managing agitation is structured according to four (or five) phases: detection/assessment, analysis, treatment, and monitoring. With this approach, the programs can help to 1) prevent agitated behavior or guide timely intervention in emerging agitation and 2) optimize the chosen treatment. Pharmacological treatment is usually considered only after psychosocial treatment is shown to be inadequate to reduce the agitated behaviors to acceptable levels. This concept is reflected in the DICE model, in which the presence of a safety risk determines, in each step, the question whether pharmacological interventions need to be considered. The IPA Workgroup observed that the threshold for employing pharmacologic therapies varied among countries and cultures, identified this as a knowledge gap, and aspired to limit cross-national practice variance by describing and recommending a uniform standard.

Management of agitation starts with an investigation of the causes of the behavior and the analysis of their setting. This can be conducted for persons who are residing in nursing homes or persons with dementia who become agitated at home. Agitated behavior may be linked to admission to a nursing home and systematic observation of behavior can begin during the admission process using standardized tools and scales. Review and analysis of the possible causes and consequences of the agitation are conducted as part of this investigation. This analysis may use the ABC approach of Antecedents of the behavior, the features of the Behavior, and the Consequences of the behavior (Teri and Logsdon, 2000). The roles of environmental, interpersonal, and psychological factors are considered. The systematic observation of the person's behavior is especially important in developing plans to prevent or reduce future episodes of agitation. Subsequently, an individual treatment plan is developed containing well-defined and measurable treatment goals; actions necessary for achieving the goals, definitions of who will perform the actions, and descriptions of when treatment effects will be evaluated. The more insight into the cause(s) and consequences of the agitation that is available, the more specific the focus and goals can be. Several care programs recommend

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

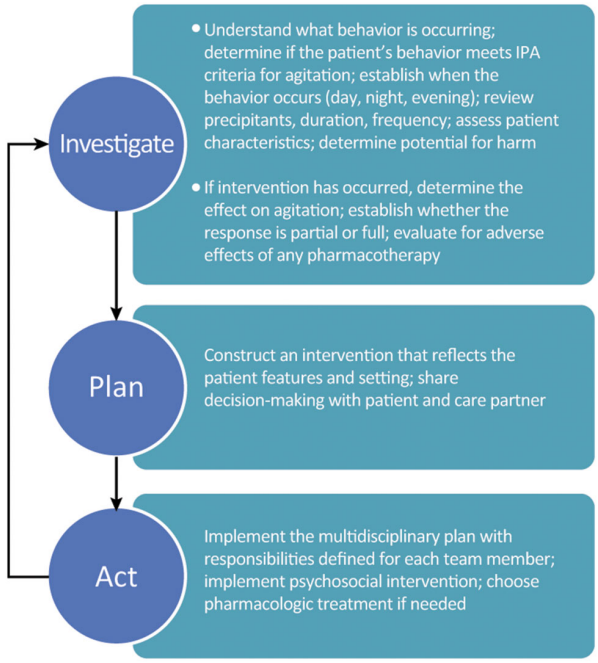

Figure 1. Investigate, Plan, Act (IPA) approach to agitation evaluation, management, and prevention. The process is repeated until the agitation is reduced to an acceptable level and prevention of recurrent episodes is optimized. The approach builds on the IPA definition of agitation in cognitive disorders (M de la Flor, PhD, illustrator).

the use of assessment tools to guide their application. After executing the treatment plan for a specific number of days or weeks, the behavior and treatment are again investigated. This may lead to adjustment of plans or goals or continuation of the plan with regular assessments.

The IPA Agitation Workgroup recommended this strategy of Investigating, Planning, and Acting (IPA) to guide the reiterative process of identifying psychosocial strategies and assessing the outcome to determine if pharmacologic interventions are needed (Figure 1). The initial investigation step builds on the IPA definition of agitation in patients with cognitive disorders (Sano, 2022). The success of each planned action is investigated. Integration of psychosocial and pharmacologic care and shared decision-making involving the clinician, staff, patient, and care partner are central to the IPA-recommended process.

Psychosocial interventions

Agitation in the home with family caregivers

Many AD patients are treated at home and family caregivers are often called upon to manage agitation, resulting in increased caregiver stress and burnout. Research regarding the content of social media posts by caregivers shows that aggressive behavior is associated with caregiver burden, exhaustion, and the feeling of wanting to give up (Bachmann, 2020). Study of blogs written by family caregivers shows that strategies for care tend to fall into six main themes: modifying the care environment, engaging the person with AD, seeking outside assistance, using complementary therapies, planning and organization, and reminiscence (Anderson *et al.*, 2019).

Brodaty and Arasaratnam (2012) examined 23 randomized controlled trials of psychosocial interventions delivered by family caregivers to address agitation and other neuropsychiatric symptoms. The meta-analysis documented a reduction in neuropsychiatric symptoms (effect size 0.34) and beneficial effects on family members (effect size 0.15). These effect sizes are comparable to those achieved with medications and without the concomitant side effects that may be associated with pharmacologic therapies. Many of the interventions focused on teaching communication skills, education and problem-solving, environmental modification and activity planning, support via web or telephone, self-care for the caregiver, and collaborative care with a health-care worker. Interventions that included multiple components, were specific to the caregiver and person with dementia, and were delivered at home with regular follow-up had the greatest success.

An alternative approach to psychosocial intervention for family caregivers is to adapt methods typically used in long-term care (LTC). Livingston *et al.*, (2014) conducted a systematic review of psychosocial randomized controlled trials for agitation, the majority of which were based in LTC. The study concluded that person-centered care, communication skills training, and dementia care mapping (DCM) reduce agitation both immediately and for up to 6 months post-intervention. DCM involves continuously observing the behavior of people with dementia and the care they receive; capturing events which lead to happiness or distress; and using these observations to improve the way people are supported. Aerobic activities and structured music therapy had immediate but not long-term effects; aromatherapy and light therapy appeared to have no or limited effect on reducing agitation (Livingston *et al.*, 2014).

Multicomponent caregiver-based interventions that include enhancing caregiver self-efficacy are beneficial in reducing patient agitation in the home setting (McDermott *et al.*, 2019; Seidel and Thyrian, 2019). Community-based programs as well as support programs play a crucial role in achieving this effect. In summary, multidimensional

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

psychosocial interventions by family caregivers for patients with mild agitation may be comparable in efficacy to pharmacological interventions.

Agitation in the nursing home

For agitation in LTC residents with dementia, the current evidence suggests that group activity-based interventions (e.g., recreation therapy), resident interventions (e.g., massage and touch therapy, music therapy), and multidisciplinary training and care (e.g., person-centered care) are the most consistently effective psychosocial treatments (Livingston *et al.*, 2014; Watt *et al.*, 2019). The systematic review by Livingston *et al.* (2014) found that both person-centered care and DCM significantly reduced agitation (Livingston *et al.*, 2014). There are caveats that may impact the efficacy of these interventions. In one study, structured activities designed by certified therapeutic recreation specialists significantly reduced agitation, but the improvements were not sustained after nursing home staff assumed planning and implementation (Buettner and Ferrario, 1997).

Psychosocial interventions that modify the environment or stimulate the senses may reduce agitation in nursing home residents with dementia. For example, snoezelen or multisensory stimulation therapy may reduce physically aggressive behaviors in nursing home residents with dementia (van Weert *et al.*, 2005).

Feasibility and scalability considerations remain barriers to widespread implementation of psychosocial interventions in LTC. Most interventions require training or supervision by specialized external staff, which may not be attainable for all nursing homes (Seitz *et al.*, 2012). Feasibility of interventions may be limited by the capabilities of individuals with dementia; sensory impairments and physical disabilities may preclude some residents from participating in interventions such as music therapy or exercise.

Limitations in research methodology and synthesis of data should be noted. For systematic reviews, the heterogeneity of study designs often rendered meta-analyses inappropriate. Many interventions were employed for residents with relatively mild agitation, and data are limited for residents with moderate and severe dementia (Na *et al.*, 2019). Other common issues among studies assessing psychosocial interventions were the small sample sizes and lack of control groups. Many studies evaluated single interventions; recent efforts have emphasized multimodal interventions.

Taken together, the literature provides evidence for the use of the psychosocial interventions described above for mild agitation in LTC.

Agitation in the ED

Older persons presenting to the ED with agitation are often cognitively impaired. For example, in one urban ED, 26% of persons over age 70 presenting for urgent care were cognitively impaired, with 10% delirious, 16% cognitively impaired without delirium, and 6% both impaired and delirious (Hustey and Meldon, 2002). In another ED study, 8.3% of persons over age 70 seeking care were delirious, the majority with hypoactive subtype and including many cases not diagnosed until ED admission (Han *et al.*, 2009). Optimal management of agitation in dementia in the ED requires accurate diagnosis of delirium as the approach to agitated delirious persons requires identification of possibly life-threatening medical disorders.

One of the major challenges of agitation management in the ED is taking a history, particularly for persons coming from an LTC environment. Information regarding the time frame of agitation, including provoking and mitigating factors and any history of prior episodes and their causes is often missing, making it difficult to know if cognitive impairment is chronic or acute and more consistent with delirium. ED protocols increasingly make use of well-validated delirium assessments such as the Confusion Assessment Method (Wei *et al.*, 2008). Other useful tools for management of delirium in the ED include the Assess, Diagnose, Evaluate, Prevent, Treat (ADEPT) tool (Shenvi *et al.*, 2020) and the Delirium Triage Screen (Shenvi *et al.*, 2020).

Older persons with agitation presenting to the ED often require pharmacologic management, but psychosocial strategies have a role in this setting. Interventions to prevent or reduce delirium in acute care environments are becoming increasingly effective: a recent Cochrane review supported the effectiveness of psychosocial interventions including reorientation (including use of familiar objects), cognitive stimulation, sleep hygiene, attention to nutrition and hydration, oxygenation, medication review, assessment of mood, and bowel and bladder care (Burton *et al.*, 2021).

Agitation in hospice

There is limited information about the treatment of hospice care-eligible patients with agitation and dementia. When treating agitation in persons with dementia, the usual first stage of treatment is to correct the medical condition that could contribute to the presence of agitation. In hospice patients, these conditions are often untreatable and/or side effects associated with treatment could be more deleterious than the agitation. Treatment goals for persons in hospice include control of symptoms and improvement of their comfort while preserving

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

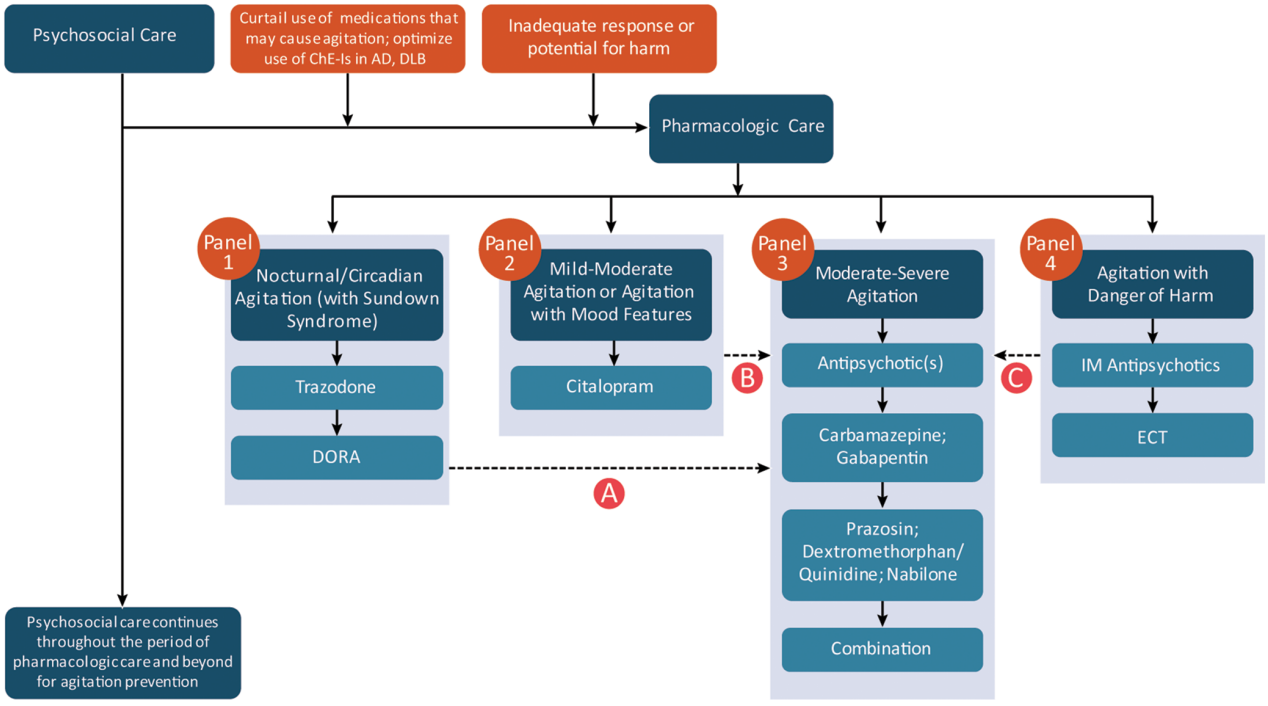

Figure 2. IPA agitation treatment algorithm. Psychosocial care is considered first and continued throughout the agitation episode with plans to curtail future agitation. Pharmacologic care is personalized and guided by the major features of the agitation including whether it has a circadian pattern or occurs mostly at night (Panel 1), is mild to moderate or has mood changes (Panel 2), is of moderate or severe severity but does not present a danger to self or others (Panel 3), or is severe and represents a treat of harm (Panel 4). Pharmacologic strategies progress from Panel 1 to Panel 3 if the first treatments fail (arrow A). Pharmacologic strategies advance from Panel 2 to Panel 3 if the first treatments fail (arrow B). Pharmacologic strategies are adjusted to Panel 3 once the very severe agitation addressed in Panel 4 is controlled (arrow C) (DORA – dual orexin receptor antagonist; ECT – electroconvulsive therapy; IM – intramuscular) (M de la Flor, PhD, Illustrator).

alertness. Controlling pain and ameliorating nausea and dyspnea are more important than uncovering and treating the potential underlying causes of agitation. Multiple metabolic changes develop in these patients as part of the dying process (Plonk and Arnold, 2005), and these may have significant effects on patient's behavior and response to treatment.

The IPA Agitation Workgroup recommends the use of psychosocial approaches as the initial step in treatment for agitated patients in hospice or who are hospice-eligible. Robust data are not available, and this recommendation is based on small studies, open-label interventions, case reports, and expert opinion. Based on preliminary evidence and given the low risk, we suggest the use of music therapy and therapeutic touch.

Integrating pharmacologic interventions into the agitation assessment and management algorithm

Pharmacologic and psychosocial approaches to agitation reduction are integrated aspects of a comprehensive approach (Figure 2). If agitation is nonurgent, intervention will begin with psychosocial approaches; pharmacotherapy may be added if the syndrome is severe and unresponsive to the initial strategies. Psychosocial treatment strategies such as caregiver education continue throughout the episode. Use of pharmacologic treatments may allow the patient to respond to psychosocial therapies, and psychosocial support may shorten the period of pharmacotherapy. If urgent intervention is needed, pharmacotherapy may be initiated in concert with psychosocial therapies in a combination treatment approach aimed at ameliorating the agitation as soon as possible and preventing relapse and future episodes.

The first step in the pharmacologic management of agitation in people with neurocognitive disorders is to review their current treatment regimen to identify drugs that may be contributing to the behavioral change. Drugs with anticholinergic effects may cause delirium (Egberts *et al.*, 2021); dopamine-blocking agents induce akathisia (Salem *et al.*, 2017); antipsychotics may precipitate neuroleptic malignant syndrome (Pileggi and Cook, 2016); serotoninergic drugs may produce a serotonin syndrome (Werneke *et al.*, 2020);

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

benzodiazepines and opioids may cause sedation, imbalance, and falls (Brandt and Leong, 2017); and stimulants may produce hyperarousal (Prado *et al.*, 2012). All of these may cause or contribute to agitation. Nearly any drug given in excess may cause delirium and agitation, and idiosyncratic reactions to drugs may produce agitation as a unique individual response.

Medical conditions such as infection, organ failure, or disorders causing pain may precipitate agitation in people with neurocognitive disorders and should be sought and appropriately treated as part of best practices in agitation management. Depression in older individuals may manifest as agitation (Hegeman *et al.*, 2012), and withdrawal syndromes associated with cessation of use of alcohol, benzodiazepine, opioids, cannabis, nicotine, and other substances should be considered as potential causes of agitation (Airagnes *et al.*, 2016). Restless legs syndrome is associated with nocturnal agitation in people with dementia (Rose *et al.*, 2011). Pharmacotherapy directed at these conditions may be essential in agitation management.

Cholinesterase inhibitors (ChE-I) and memantine reduce agitation and psychosis in some persons with AD dementia or dementia with Lewy body patients; optimizing the dose and adherence to the treatment regimen of these agents is an important step in the pharmacologic management of agitation, especially in people whose agitation is not severe or in urgent need of treatment. These agents may also reduce the emergence of agitation in agitation-prone people, contributing to agitation prevention. Cholinesterase inhibitors are generally not effective in reducing acute or severe agitation (Howard *et al.*, 2007).

The IPA agitation reduction and prevention algorithm is based on published evidence, previous best practice guidelines, and expert opinion (Figure 2). The approach builds on the IPA definition of agitation (Sano, 2022). There are no approved treatments for agitation in the USA, and all prescribing is "off label." Risperidone is approved for behavioral and psychological symptoms of dementia in Australia, Canada, United Kingdom, and New Zealand (Yunusa and El Helou, 2020) and for aggression in persons with AD in Norway. There are relatively few studies of pharmacotherapy for agitation in patients with neurocognitive disorders, and studies that would inform comparative effectiveness, sequential application, or concomitant use of potential treatments are scarce. Many of the studies with these agents were conducted before contemporary trial standards evolved.

The IPA Agitation Workgroup organized interventions into panels of agents that can be considered for the treatment of agitation emerging in a variety of circumstances and exhibiting several levels of severity (Figure 2). Choices within each panel are guided by emerging evidence, individual patient characteristics (e.g., parkinsonism), the person's history of treatment response, and the clinician's experience with the available agents. Best practices for pharmacotherapy with psychotropics require treating with the lowest effective doses, periodic withdrawal if symptoms have been controlled for several months, vigilance for side effects, and shared decision-making with individuals with dementia and their care partners regarding the potential for benefit and the possibility of harm associated with pharmacotherapy.

Panel 1 presents pharmacotherapies for agitation that occurs primarily at night or has a circadian pattern such as "sundowning" with periods of agitation in the afternoon and early evening. Trazodone is commonly used in nighttime behavioral disturbances and may be tried as an initial option (Ringman and Schneider, 2019). Dual orexin antagonists are an alternative for insomnia in dementia, and suvorexant and lemborexant have been shown to improve insomnia in people with AD (Herring *et al.*, 2020; Moline *et al.*, 2021). Evidence is mixed for the use of melatonin in the setting of nighttime agitation and sundown syndrome; it may warrant a trial in some circumstances (Cohen-Mansfield *et al.*, 2000). Benzodiazepine hypnotics should be avoided in people with neurocognitive disorders given the increased risk of sedation, falls, and fractures they pose. If the agitation does not respond to therapies of Panel 1, the approaches outlined in Panel 3 are implemented.

Panel 2 summarizes interventions for people with dementia and mild-moderate agitation or who have agitation with evidence of a mood disturbance. Citalopram is the most well-studied agent in this panel and has been shown to reduce agitation in AD (Porsteinsson *et al.*, 2014). Persons with more mild dementia and moderate levels of agitation responded best to treatment with citalopram (Schneider *et al.*, 2016). Worsening cognition and QT interval prolongation were observed with citalopram at the dose studied in the trial (30 mg/day). Evidence regarding the efficacy of mirtazapine in reducing agitation is mixed; a recent study found no effect on agitation and preliminary evidence of increased mortality associated with this treatment (Banerjee *et al.*, 2021). If individuals with agitation fail to respond to one or more of these agents, use of the drugs described in Panel 3 is the next step in agitation management.

Panel 3 describes agents used for moderate to severe agitation that does not require emergent therapy to control the threat of harm by the person with dementia to themselves or their care partners. Atypical antipsychotics are the most used agents in

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

this setting. Risperidone (Brodaty *et al.*, 2003), olanzapine (Street *et al.*, 2000), aripiprazole (Yunusa *et al.*, 2019), and brexpiprazole (Grossberg *et al.*, 2020) reduced agitation in double-blind placebo-controlled studies. Quetiapine is frequently used for the treatment of agitation; evidence of its effectiveness is mixed. In some circumstances such as agitation in patients with dementia with Lewy bodies parkinsonism may be greatly exaggerated by antipsychotics and other agents should comprise the first-line intervention (Kyle and Bronstein, 2020). Pimavanserin is approved for the treatment of psychosis in Parkinson's disease and appears not to produce extrapyramidal effects (Cummings *et al.*, 2014). This agent reduced agitation in persons with AD and psychosis if the psychosis responded to treatment (Ballard *et al.*, 2020).

When antipsychotics are found to be ineffective or the response is insufficient, mood-stabilizing anticonvulsants may be of benefit in reducing agitation. Carbamazepine and gabapentin are the two agents most prescribed for agitation (Olin *et al.*, 2001; Supasitthumrong *et al.*, 2019). Valproic acid has been used for the treatment of agitation in dementia; most studies show no benefit compared to placebo (Herrmann *et al.*, 2007). A recent trial of low-dose lithium found that the therapy did not reduce agitation (Devanand *et al.*, 2022).

An alternative to mood-stabilizing anticonvulsants for antipsychotic-resistant agitation, is prazosin, an alpha-1 adrenoreceptor antagonist. This agent reduced agitation in a well-conducted trial (Wang *et al.*, 2009). A Phase 2 trial of dextromethorphan and quinidine demonstrated reduced agitation in both phases of a sequential parallel comparison design trial (Cummings *et al.*, 2015b). Nobilone, a synthetic cannabinoid reduced agitation in a randomized controlled trial of persons with AD and agitation; sedation was more common with nobilone than placebo (Herrmann *et al.*, 2019).

Agents in Panel 3 may be used sequentially or in combination as augmentation approaches. Side effects may be more common with combination regimens and vigilance regarding patient safety and tolerance is required.

In a few cases, agitation is extreme, and there is danger that the person with dementia may harm themselves or others. In such cases, the use of oral agents may be inappropriate or impossible and use of intramuscular therapies with a faster onset of action is warranted. Panel 4 outlines the approach that can be used in these circumstances. Intramuscular formulations of olanzapine and of aripiprazole have been shown in controlled trials to reduce agitation in dementia (Meehan *et al.*, 2002; Rappaport *et al.*, 2009). Shared decision-making is critically important when the autonomy of the individual is curtailed by the intervention strategy. Regulation of the use of these medications varies across countries. When these agents fail or produce unacceptable side effects, electroconvulsive therapy (ECT) can be considered as an alternative approach to the treatment of severe agitation (Hermida *et al.*, 2020). Data supporting use of ECT in this setting are drawn from case series, clinical observations, and retrospective chart reviews. Once agitation has resolved at least partially, the person can be treated with the agents in Panel 3.

In addition, to the agents presented in Panels 1–4, other pharmacologic interventions are sometimes indicated in specific clinical circumstances. The use of benzodiazepines may occasionally be indicated for short-term use and intramuscular lorazepam has the benefit of a relatively short time to onset; it can be considered as an alternative to intramuscular antipsychotics. In individuals experiencing pain, use of morphine may reduce agitated behaviors (Husebo *et al.*, 2014). Morphine might be an advantageous choice for persons in hospice with painful conditions. Clinicians should be aware of the potential side effects of opioids including constipation, pruritus, increased sleepiness, dry mouth, and anorexia. Another alternative that is available for persons in hospice is delta-9-tetrahydrocannabinol (delta-9-THC), the most biologically active isomer of (-)-trans-D-9-tetrahydrocannabinol. This is a psychoactive compound that activates cannabinoid receptors (mainly CB1 type) (Wiffen *et al.*, 2014). THC use has been reported to decrease or modulate anxiety, fear-related behaviors, and disabling thoughts of death. A retrospective review found evidence that dronabinol (an FDA-approved form of THC) reduced agitation in AD (Woodward *et al.*, 2014). Cannabidiol (CBD), a nonpsychoactive component of the marijuana plant, has been observed to have therapeutic effects on anxiety, appetite, sleep, pain perception, nausea, and vomiting which may be beneficial in persons in hospice with agitation.

Conclusion

The IPA Agitation Work Group formulated an integrated algorithmic approach to best practices for the reduction and prevention of agitation based on data from randomized trials, clinical observations, published guidelines, previous algorithms, and expert knowledge. The IPA approach to agitation emphasizes the importance of an Investigation, Planning, and Acting (IPA) framework for all interventions considered for patients with agitation. We stress the importance of psychosocial approaches with and without pharmacologic therapies and

https://doi.org/10.1017/S104161022200103X Published online by Cambridge University Press

emphasize individualized treatment planning based on the characteristics of the agitation and setting of the patient. Multimodal psychosocial interventions including both patient and care partner may reduce agitation to acceptable levels. Pharmacotherapy may be required for the reduction of agitation in some persons with dementia. We stress the importance of an assessment cycle using a systematic treatment plan with vigilance for both effectiveness and side effects, thoroughly considering the balance of benefit and harm. The foundation of the IPA algorithm is the IPA consensus definition of agitation in cognitive disorders (Sano, 2022); the algorithm is intended as a tool for clinicians to operationalize the definition in management of persons with cognitive impairment and agitation.

Conflicts of interest

J. Cummings has provided consultation to Acadia, Alkahest, AlphaCognition, AriBio, Biogen, Cassava, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lilly, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, Prothena, ReMYND, Resverlogix, Roche, Signant Health, Suven, and United Neuroscience pharmaceutical, assessment, and investment companies. He is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; NIA grant P20AG068053; NIA grant P30AG072959; NIA grant R35AG71476; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; and the Joy Chambers-Grundy Endowment.

M. Sano receives grant support from NIH/NIA (P30AG066514, R24AG065163, and R01AG051545) has provided consultation to Eisai, Avenir, vTv, Biogen, BioXcel, F. Hoffman LaRoche Merck NovoNordisk and Novartis and is the chair of the DSMB for a Phase II Trial to Evaluate Safety and Efficacy of GM-CSF/Sargramostim in Alzheimer's Disease (SESAD) (sponsor: University of Colorado); Alzheimer Association Member of Medical and Scientific Advisory Group.

S. Auer was supported by grants of the Austrian Science Fund (FWF; I 2361-B27), the Federal State of Lower Austria (K3-F-907/001-2020) and has no financial relationships to disclose.

S. Bergh has no disclosures.

C. Fischer receives funding from Brain Canada, the Weston Foundation, NIH, Vielight Inc. and Hoffman La Roche and has no financial relationships to disclose.

D. Gerritsen has no financial relationships to disclose.

G. Grossberg is a consultant to Acadia; Avanir; Axsome; BipXcel; Biogen; Genentech; Karuna; Lundbeck; Otsuka; Roche; Takeda and he receives research Support from HRSA; NIA; Functional Neuromodulation; He is also a member of Safety Monitoring Committees for Anavex; EryDel; Intra-Cellular; Merck; Newron.

Z. Ismail has received honoraria from Lundbeck/Otsuka. His institution has received fees from Acadia, Biogen, and Roche.

K. L. Lanctôt is supported by the Alzheimer's Drug Discovery Foundation (ADDF) and the Bernick Chair in Geriatric Psychopharmacology, has provided consultation to BioXcel Therapeutics, Bright Minds, Cerevel Therapeutics, Eisai Co. Ltd., ICG Pharma, Jazz Pharmaceuticals, Otsuka, Kondor Pharma, H Lundbeck A/S, Merck Sharp Dohme, Novo Nordisk, Praxis Therapeutics.

M. I. Lapid, MD was supported in part by grants R01AG061100 from the National Institute on Aging and has no financial relationships to disclose.

J. Mintzer is a consultant for Acadia Pharmaceuticals, Genentech, Ironshore Pharmaceuticals, Praxis Bioresearch, and Sygnature Discovery and a Steering Committee Member/Association Member for the Alzheimer's Clinical Trials Consortium, the International Psychogeriatric Association, and the Technology Accelerator Company and a majority partner for Recruitment Partners and a Stockholder and VP of Clinical Affairs for NeuroQuest.

R. Palm has no disclosures.

P. B. Rosenberg, M.D. was supported in part by grants R01AG054771 and R01AG050515 from the National Institute on Aging and has no financial relationships to disclose.

K. Zhong has no disclosures.

M. Splaine has no disclosures.

C. Zhu has no disclosures.

Description of authors' roles

All authors are members of the IPA Agitation Work Group. All authors participated in conceptualizing, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

Acknowledgements

JC is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; NIA grant P20AG068053; NIA grant P30AG072959; NIA grant R35AG71476; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment for the Pam Quirk Brain Health and Biomarker Laboratory; and the Joy Chambers-Grundy Endowment.

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