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Emergent and Non-Emergent Agitation in the Older Adult: Evaluation and Management

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Abstract

Purpose of Review This paper aims to describe the heterogenous presentation of agitation in older adults. It will delve into semiology, diagnosis, classification, as well as treatment options available to address agitation.

Recent Findings Agitation is a common and distressing symptom that poses risk to patients and caregivers. In older adults, it is often a manifestation of medical and neuropsychiatric conditions such as dementia, stroke, delirium, psychiatric disorders, catatonia, substance intoxication or withdrawal. Agitation in dementia is defined as excessive motor behavior and verbal or physical aggressive behavior, causing significant disability. Several tools are used to describe it; most notably, the Cohen-Mansfield Agitation Inventory (CMAI). Its evaluation is most complete with the DICE (Describe, Investigate, Create, Evaluate) approach which allows for examination of precipitating factors such as delirium, psychiatric disorders, pain, polypharmacy, constipation, environmental elements, and others. Non-pharmacological management should be attempted first, tailoring the treatment to the precipitants. If these fail, pharmacological treatments, although inherently risky, include non-emergent and emergent options. The former are antidepressants and cognitive enhancers, and the latter include antipsychotics, trazodone, and electroconvulsive therapy (ECT). Benzodiazepine use should be limited to excited catatonia or alcohol withdrawal.

Summary Agitation management is as much about addressing unmet needs as it is about treatment of underlying etiologies. A careful and systematic approach is imperative to successful treatment. It allows the clinician to uncover what the patient is unable to convey and minimizes the risk that polypharmacy may bring. More research is needed into methods to quantify, anticipate, and safely treat agitation in older adults.

Keywords Agitation · Geriatrics · Geriatric psychiatry · Dementia · Delirium

Introduction

According to data from the National Center for Health Statistics, during 2014–2017, approximately 20% of all emergency department visits in the United States were made by adults aged 60 and over [1]. As the population of older adults grows to a predicted 98 million by the year 2060, rates of dementia are also projected to rise, and an increase in emergency department utilization by this group will likely follow [2]. Agitation is a common concern for which older adults present to the emergency department. Older adults with agitation are brought to the emergency department when behaviors can no longer be safely managed at home or in a long-term care facility [3]. In older adults, agitation often manifests within the context of an underlying medical and/or neuropsychiatric condition, such as dementia, stroke, delirium, psychotic disorder, catatonia, substance intoxication or withdrawal [4]. When specifically related to dementia, agitation leads to poorer overall outcomes for patients and caregivers [5]. The rate of cognitive and functional decline increases as well as the rate of economic and social burden for the caregivers.

Agitation which is disruptive, aberrant, or bothersome but does not place anyone in imminent danger is considered "non-emergent" and can be managed in the ambulatory setting over

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the course of days to weeks [6]. Non-pharmacological strategies for managing non-emergent agitation in older adults are considered first-line and include behavioral and environmental modifications and medical interventions [6]. If such interventions have been utilized and the behavior escalates, placing the patient and/or others at imminent risk of harm, the agitation should be considered "emergent," necessitating rapid de-escalation [6]. In these cases, time-limited pharmacological management is often needed, but only after careful consideration of the risks and benefits associated with use and close monitoring for adverse side effects [7]. Meta-analyses have evaluated the use of antipsychotics, benzodiazepines, anticonvulsants, and antidepressants, and some agents have shown efficacy over placebo for favorable behavioral outcomes [8]. However, there are limited data to support the safety of these agents in terms of mortality outcome measures, hence the lack of FDA-approval for this indication [7].

This article describes the identification, classification, and evaluation of agitation in older adults as well as which treatment modalities may be appropriate for short-term versus long-term management. The risks and benefits of different treatment modalities will be reviewed, including non-pharmacologic and pharmacologic as well as emergent and non-emergent. While this article focuses primarily on agitation associated with cognitive impairment, many of the proposed strategies can be applied to agitation secondary to any medical or neuropsychiatric condition.

Clinical Presentation

The term agitation is a broad umbrella-term that has been variably and vaguely defined. The term may be used to describe presentations ranging from repeated questioning to physical aggression. It follows the heterogenous nature of disruptive behaviors across cognitive impairment and as such requires very specific description of the behavior to adequately define and treat it. In line with recent consensus criteria [9], we define agitation as excessive motor behavior or verbally or physically aggressive behavior causing significant disability. Disability could be within interpersonal relationships, other aspects of functioning, or interfere with patients' ability to perform and participate in activities of daily living.

Using the framework established by the Cohen-Mansfield Agitation Inventory (CMAI), agitation can be clustered into physically aggressive agitation, physically nonaggressive agitation, verbally aggressive agitation, verbally nonaggressive agitation [10]. The CMAI allows for screening and frequency monitoring of 29 distinct behaviors (Table 1) [10]. A recently validated observational variant of the CMAI has also shown promising results in using this tool by observants who are not familiar with the subject [11].

Evaluation of the Older Adult with Agitation

In 2011, a multidisciplinary expert panel developed the Describe, Investigate, Create, Evaluate (DICE) approach for evaluating and treating neuropsychiatric symptoms of dementia [12]. Although developed specifically for patients with dementia, this general framework can be useful for evaluating any older adult with agitation—dementia, after all, is underdiagnosed, particularly in non-white individuals [13]. Using the DICE approach, witnesses to the behavior such as caregivers, staff, or the patient themselves if possible, should first describe the behavior.. It is important to determine whether there is a known diagnosis of dementia or cognitive impairment, the time course/chronology of the behavior, the severity of the behavior, and the individual's premorbid personality. Since agitation encompasses a broad range of problematic behaviors, a number of rating scales have been developed, including the CMAI described above [14–16], the Overt Agitation Severity Scale (OASS) [17], the Behavioral Activity Rating Scale (BARS) [18], and the Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) [19]. Some scales are more suited to certain settings than others: the BARS, for example, is easy to complete and can be used in a nonmedical setting, such as an assisted living center [20], while the NPI-C must be completed by a clinician.

Next, possible underlying causes of the behavior, such as dementia [21, 22], delirium [23], depression [24], pain, constipation [25], and environmental factors [12] should be investigated. Delirium is notoriously underdiagnosed despite having an occurrence rate between 11 and 42% per admission [26]. Delirium is caused by an acute medical illness or substance/drug effect [23, 27, 28], the latter risk compounded by high rates of polypharmacy in the geriatric population [29]. Delirium often presents similarly to dementia but is differentiated by its acute, fluctuating, and typically reversible nature. Collateral history obtained from caregivers regarding the patient's baseline personality and cognitive abilities can be helpful in differentiating delirium from dementia [30]. Moreover, delirium is often superimposed on dementia: a prospective cohort study of geriatric patients admitted to a Scotland hospital found that almost half of patients with known dementia developed delirium during their admission [31]. Primary psychiatric disorders such as depression can also present with agitation, particularly in older adults [32]. Given their cognitive challenges, patients with dementia are less able to communicate their pain and are thus often undertreated, leading to prolonged distress and agitation [25]. Treating pain in older adults, such as in the postoperative setting, can be challenging given the age-associated changes in opioid pharmacokinetics and pharmacodynamics and unwanted side effects such as nausea, constipation, urinary retention, and pruritis, all of which can themselves lead to agitation [33]. Environmental factors may also be a source of agitation. The constant bustle of the emergency room

Table 1 Behaviors of Agitation in the Older Adult[1]

Agitation Category	Behaviors
Physically aggressive behavior	Hitting
	Biting
	Kicking
	Pushing
	Grabbing onto people
	Scratching
	Spitting
	Making physical sexual advances
	Hurting self or others
	Throwing things
	Tearing things or destroying property
Physically nonaggressive behavior	Paces, aimless wondering
	Inappropriate dress or disrobing
	Trying to get to different places
	Hiding things
	Hoarding things
	Intentional falling
	Eating/drinking inappropriate substances
	Handling things inappropriately
	Performing repetitious mannerisms
	General restlessness
Verbally aggressive behavior	Screaming
	Making verbal sexual advances
	Cursing or verbal aggression
Verbally nonaggressive behavior	Repetitive sentences or questions
	Strange noises (like weird laughter or crying)
	Complaining
	Negativism
	Constant unwarranted request for attention or help

[1] Adapted from the Cohen-Mansfield Agitation Inventory (CMAI) [12]

may be overstimulating, or conversely the patient may not have access to their hearing aids, leading to increased confusion. Behaviors that occur at home but stop upon admission to the hospital suggest that the home environment may be a source of agitation, perhaps due to increased caregiver burden leading to confrontational interactions or even elder abuse [12, 34–37].

Given the broad differential for agitation in the older patient, it is important to perform a careful physical exam, including vital signs and a neurological exam, as well as obtain laboratory data such as blood electrolyte and glucose levels, complete blood counts, and a urinalysis. Imaging or electroencephalogram (EEG) may be necessary as well in the case of suspected trauma/stroke or seizure, respectively. It is important to quickly obtain these objective data, since an agitated presentation along with other factors such as baseline cognitive impairment or lack of collateral information from caregivers may prevent obtaining a detailed history. Objective data should also be interpreted carefully in older adults: infection, for example, is known to present differently in this population due to age-related changes in the immune system and thermoregulation amongst other factors [38]. Substance use or withdrawal are often overlooked causes of agitation in older patients. A patient who becomes agitated days after surgery could be undergoing alcohol withdrawal; a sudden change in vital signs would be an important clue [39]. A medication inventory, including over the counter medications and supplements, should be taken for all patients, since delirium-inducing medications like benzodiazepines, non-benzodiazepine hypnotics, tricyclic antidepressants, and other medications with anticholinergic properties continue to be prescribed to older adults [40].

Older patients can develop agitation in a variety of settings, from the emergency department to the surgical service. It is therefore crucial for all medical providers to begin the evaluation of the agitated older adult as soon as possible so as to not delay workup and treatment. Psychiatric evaluation is recommended if non-pharmacological management is insufficient

and pharmacological interventions must be initiated. In these cases, early involvement by a geriatric specialist such as a geriatrician or geropsychiatrist is critical to avoid interventions that may be harmful to the elderly. A virtual consultation with these specialists may be an option in resource-limited healthcare settings. A formal psychiatric evaluation may also help with clarifying diagnosis, which would aid disposition planning. Determining the disposition of the acutely agitated patient—i.e., medical or psychiatric admission—can be complicated, with transfers between medical and psychiatric services even more so, with potential for bias. A study of transfers to a psychiatric hospital in Greece, for example, suggested that patients on medical or surgical services with poor family support or an existing psychiatric diagnosis were more likely to be transferred to psychiatry [41].

In general, patients with an acute medical illness requiring treatment should be admitted to a medical service, while patients whose agitation is likely due to underlying dementia or a primary psychiatric disorder can be admitted to a psychiatric service if there is an immediate risk of harm. Regardless of where the patient is admitted, disposition planning should begin immediately, since older patients with behavioral symptoms are likely to require a higher level of care upon discharge [27]. If the patient requires the appointment of a legal guardian, this process should be initiated quickly, since petitioning the courts can prolong the patient's length of stay, with the risk of additional hospital-acquired complications [42].

Non-Pharmacologic Management

Using the DICE approach, the next steps in managing agitation include creation and evaluation of a comprehensive treatment plan. Agitation in the older adult that does not pose a threat of immediate harm should be managed with non-pharmacologic strategies before attempting pharmacologic treatment. This includes eliminating triggers specific to the patient, improving sleep hygiene, and supporting the caregiver [12]. Abraha et al. conducted a systematic overview of non-pharmacologic treatments for behavioral symptoms in dementia. The strongest evidence exists for the use of music therapy to reduce agitation, aggression, and anxiety, as well as formal caregiver training and dementia care mapping, in which caregivers attempt to place themselves in the shoes of the patient with dementia—especially when supervised by a healthcare professional [43, 44]. While a variety of other non-pharmacological therapies exist, these have limited proven efficacy, possibly due to the relative heterogeneity of their implementation compared to pharmacologic treatments [43]. Non-pharmacologic treatment strategies should be tailored to the individual patient. A lifelong pet owner, for example, may show improvements in behavioral symptoms after a session of pet therapy, despite the overall evidence basis for pet therapy being weak. Interventions as simple as providing amplifiers to patients who are hearing impaired may improve anxiety levels during hospitalizations. Ultimately, the successful implementation of non-pharmacologic interventions requires time and creativity: time for the care team to get to know the patient and caregivers and creatively modify the patient's hospital experience to reduce stressors and bring to them some of the joy from the outside world [12]. Simple interventions may include giving the patient a doll, playing music familiar to the patient, assigning the patients tasks that highlight the abilities they have retained like folding towels, helping to organize the bed, or drawing.

Not all non-pharmacologic interventions for agitation are without risk. The use of physical restraints has come under significant criticism due to ethical concerns as well as the risks, including falls, fractures, and decubitus ulcers from immobilization [45]. A cohort study of patients in the intensive care unit found that of patients who had been physically restrained, almost 40 % developed delirium, with the risk increasing by over twenty-six times when patients were restrained for six days or more [46]. A cross-sectional study of patients presenting to the emergency department with agitation identified two clusters of patients for whom physical restraints were often used: younger males with psychiatric illness and/or substance use and those experiencing homelessness and older adults presenting with medical concerns who did not follow commands [47]. Patients are more likely to be restrained in the emergency department than on an inpatient unit [48]; prioritizing the transfer of older patients from the emergency department would likely mitigate these harmful effects, while also reducing the incidence of delirium [49].

Another non-pharmacological intervention that has come under scrutiny is the practice of seclusion. A study of patient experiences in psychiatric settings revealed that being placed in seclusion had almost the same likelihood of being "severely or extremely distressing" to these patients as being placed in restraints [50]. Unlike pharmacological options for sedating severely agitated patients, restraints and seclusion carry the risk of being used for longer than necessary, especially in a busy hospital setting. Given the risks of injury and overuse and the availability of pharmacological options for rapid sedation in emergencies, restraint and seclusion should be avoided whenever possible.

Pharmacological Management and Neuromodulation

Although non-pharmacological interventions for agitation are decidedly safer than pharmacological ones, patients who pose an immediate threat to themselves or others or whose agitation compromises necessary medical care will likely require the latter. Pharmacologic treatment should also be considered in

patients who fail non-pharmacologic interventions and in those who have an underlying primary psychiatric disorder. Medications that can be used to treat agitation in older adults include antipsychotics, antidepressants, and sedatives, although it is important to note that no medications are FDA-approved for agitation. Each class of medication has various degrees of evidence basis, benefits, and risks. Treatment response should be monitored with the agitation scales described above.

For patients with dementia and/or an underlying psychotic disorder, the antipsychotics risperidone, olanzapine, and aripiprazole can be effective in treating behavioral symptoms. Quetiapine, while often used in clinical practice, has a poorer evidence base for use in patients with dementia [5]. One advantage of quetiapine is that it has a lower risk of inducing extrapyramidal symptoms (EPS) compared to risperidone and olanzapine [51] and therefore may be a better medication for patients with diagnosed or suspected synucleinopathy such as Parkinson's disease or Lewy body dementia. Antipsychotics as a class have come under scrutiny for increasing the risk of cardiovascular events and mortality in patients with dementia. Compared to risperidone, ziprasidone and quetiapine appear to have a lower risk of these major adverse cardiovascular events [52]. Haloperidol, a common and relatively cost-effective [53] first-generation antipsychotic used to treat acute agitation, has a higher risk of major cardiovascular events in these patients and should be avoided in the geriatric population given the risk of EPS as well [52]. If absolutely necessary, haloperidol should be given at the low dose of 0.5 mg; higher doses do not appear to reduce the duration of agitation but do however increase the risk of side effects [54]. The atypical antipsychotic olanzapine can be given by mouth or sublingually with an onset of 15–120 min. If a more rapid response is required, it can be given intramuscularly or intravenously with an onset of 15–30 min. For patients with a diagnosed synucleinopathy, quetiapine has an onset of 30–90 min; for rapid treatment in this population, lorazepam can be given intramuscularly or intravenously, though benzodiazepines carry their own risks [2]. Given the risks of antipsychotic use in patients with dementia, they should be reserved for periods of acute or severe agitation with consideration given to taper and discontinue once the patient has achieved a period of behavioral stability. Some patients with severe behavioral symptoms may relapse upon antipsychotic discontinuation [5], at which time a decision should be made regarding risks and benefits of long term antipsychotic treatment.

The atypical antidepressant trazodone has sedative properties and improves sleep parameters but does not consistently improve agitation in patients with dementia; anecdotally, we find that it can be helpful on an "as needed" basis for non-emergent agitation. It is also possible that in certain patients for whom lack of sleep is the primary cause of their agitation, trazodone may be effective in reducing agitation. Anticonvulsants such as valproic acid, carbamazepine, and gabapentin do not consistently improve agitation in patients with dementia but do have many adverse effects; therefore, we recommend against their routine use in the absence of an underlying bipolar disorder. A randomized clinical trial has been designed to evaluate the use of lithium to treat agitation and aggression in patients with Alzheimer's disease [55].

Benzodiazepines are commonly used to treat agitation in patients with dementia, but no meta-analytic data demonstrate efficacy in these patients [5]. The use of benzodiazepines in older adults is fraught with complications such as delirium, falls, and fractures, and should be avoided [40, 56]. Exceptions include catatonia and alcohol withdrawal. The excited type of catatonia presents with symptoms ranging from agitation to autonomic dysfunction and can be deadly if left untreated [57, 58]. Benzodiazepines, often administered parenterally, are effective in treating acute catatonia [59]. Alcohol withdrawal syndrome, an often-overlooked diagnosis in older patients, can also present with agitation and autonomic symptoms. Benzodiazepines have been the standard treatment for alcohol withdrawal for decades with a wealth of evidence showing their safety and efficacy when used for this purpose [60, 61].

When patients with dementia become severely agitated and fail pharmacological treatment, another option is electroconvulsive therapy (ECT). A systematic review of the evidence for ECT being used for this purpose suggested that most patients show early benefit with few side effects. However, none of the included studies were randomized control trials and suffer from selection bias [62]. The only prospective study included in this review did not follow a control group, such as pharmacotherapy only, limiting the strength of its findings [63]. Numerous studies have attested to the safety of ECT in various geriatric patient populations [64], but large randomized studies are still needed.

Non-Emergent Pharmacologic Management

Antidepressants, the first line pharmacologic treatment for older adults with depression and anxiety disorders, have a slow onset of action but can also be used in the long term to treat symptoms of agitation in patients with dementia. Selective serotonin reuptake inhibitors (SSRIs) like citalopram and sertraline are effective at reducing agitation [5]. A clinical trial of citalopram for treating neuropsychiatric symptoms in patients with Alzheimer's disease found that the subgroup of patients with primarily affective symptoms benefited most. However, there were troublesome side effects such as QT prolongation and cognitive worsening [65], which further studies found to be associated with the R-enantiomer of the drug, while the S-enantiomer was associated with the most benefits [66]. Hence, a trial was designed for the use of escitalopram in this

population [67]. Prior to initiating citalopram in older patients, it would be helpful to obtain a baseline electrocardiogram and monitor QT interval periodically.

There is emerging evidence that cannabinoids may be useful in treating agitation in older adults with dementia. A double-blind crossover randomized control trial demonstrated the efficacy of nabilone, a synthetic oral tetrahydrocannabinol (THC) analogue that acts as a partial agonist at CB1/2 receptors, in reducing agitation in patients with moderate-to-severe Alzheimer's disease over a six-week long treatment period [68]. Notably, nabilone was superior to risperidone [69], SSRIs, trazodone [70], and other cannabinoids like THC [71] and dronabinol [72], a full agonist at CB1/2 receptors. However, this trial did note the frequent side effect of sedation, possibly due to the advanced age of the participants, but with no worsening of cognitive function. Only 38 patients were included in this trial, but its results offer a promising alternative to other pharmacological options [68]. Dextromethorphan-quinidine, an approved treatment for pseudobulbar affect, is another candidate medication for the treatment of agitation in patients with dementia [73]. A randomized controlled trial comparing dextromethorphan-quinidine to placebo did reveal an increased risk of falls in patients taking this medication but no increased risk of sedation, cognitive impairment, or QT prolongation [74]. Further studies are needed to confirm its safety and efficacy in the elderly population.

Cholinesterase inhibitors and the NMDA glutamate receptor antagonist memantine are other options for treating non-emergent agitation in patients with dementia [75]. Cholinesterase inhibitors may be particularly helpful for patients with Alzheimer's disease or Lewy body dementia [76]. A randomized controlled trial conducted over a twelve-month period found that patients with Alzheimer's disease receiving memantine, rivastigmine, or donepezil, but not galantamine, experienced significant improvement in their neuropsychiatric symptoms [77]. A retrospective study found that six months of treatment with memantine in addition to a cholinesterase inhibitor resulted in improvement in agitation scores in 80% of patients [78]. Cholinesterase inhibitors as well as memantine can have some unpleasant side effects such insomnia and gastrointestinal distress but are otherwise generally well-tolerated [75].

Table 2 summarizes pharmacologic treatment options for emergent and non-emergent agitation, with available routes and recommended dosing in the geriatric population [75, 79–82] For patients who are more frail, suggested by their body mass index (BMI), vital signs, mobility, comorbidities, or medications, the lower dose is recommended [79].

Table 2 Medications for Agitation in the Older Adult [74, 78–81]

Class	Medication	Route	Recommended Dosage
Antipsychotics	Risperidone	Oral or rapid dissolving	Starting dose: 0.25–0.5 mg/day Maximum 1–2 mg/day
	Aripiprazole	Oral	Starting dose: 2.5 mg/day
	Quetiapine	Oral	Starting dose: 12.5–25 mg/day Maximum: 150–300 mg/day
	Olanzapine	Oral, rapid dissolving, intramuscular, intravenous	Starting dose: 2.5 mg/day Maximum dose: 10 mg/day
Antidepressants	Citalopram	Oral	Starting dose: 5–10 mg/day Maximum dose: 20 mg/day
	Escitalopram	Oral	Starting dose: 5 mg/day Maximum dose: 10 mg/day
	Sertraline	Oral	Starting dose: 25 mg/day Maximum dose: 200 mg/day
	Trazodone	Oral	Starting dose: 12.5–50 mg/day Maximum dose: 200 mg/day, often divided doses
Cholinesterase Inhibitors	Donepezil	Oral	Starting dose: 5 mg/day Maximum dose: 10 mg/day (4–6 weeks after initiation)
	Rivastigmine	Oral or transdermal patch	Starting dose: 3 mg/day (oral) or 4.6 mg/day (patch) Maximum dose (oral): 12 mg/day Maximum dose (patch): 13.3 mg/day
	Galantamine	Oral	Starting dose: 8 mg/day Maximum dose: 24 mg/day
NMDA Receptor Antagonist	Memantine	Oral	Starting dose: 5 mg/day (immediate-release) or 7 mg/day (extended-release) Maximum dose: 20 mg/day (immediate-release) or 28 mg/day (extended-release)

Conclusion

Agitation in the older adult is a common concern with significant consequences, particularly for patients with neurocognitive disorders and their caregivers. Management of agitation begins with the identification and description of the specific behaviors of concern, ideally using validated rating scales, followed by a thorough evaluation to identify potential unmet needs and contributing factors. The treatment of agitation should be tailored to the individual, beginning with non-pharmacologic management, including addressing any underlying contributors and providing caregiver education and support. Pharmacologic and neuromodulation treatment options have shown some efficacy though none are FDA-approved, and risks/benefits must be carefully weighed. Effects of treatment should be monitored and the need for medication re-evaluated periodically. As is frequently the case in caring for complex older adults with neuropsychiatric illness, a systematic, biopsychosocial approach by a multidisciplinary care team can ensure patient-centered care in the optimal setting.

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