


REVIEW ARTICLE

Geriatrics

The agitated older adult in the emergency department: a narrative review of common causes and management strategies

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"The Agitated and Combative Older Patient in the Emergency Department: Management Strategies and Potential Pitfalls," presented at the Annual Meeting of the Society of Academic Emergency Medicine, May 17, 2018, in Indianapolis, Indiana by Alexander Lo, MD, PhD, Maura Kennedy, MD, MPH, and Michael LaMantia, MD, MPH.

Funding and support: By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Abstract

Agitation and aggression are common in older emergency department (ED) patients, can impede the expedient diagnosis of potentially life-threatening conditions, and can adversely impact ED functioning and efficiency. Agitation and aggression in older adults may be due to multiple causes, but chief among them are primary psychiatric disorders, substance use, hyperactive delirium, and symptoms of dementia. Understanding the etiology of agitation in an older adult is critical to proper management. Effective non-pharmacologic modalities are available for the management of mild to moderate agitation and aggression in patients with dementia. Pharmacologic management is indicated for agitation related to a psychiatric condition, severe agitation where a patient is at risk to harm self or others, and to facilitate time-sensitive diagnostic imaging, procedures, and treatment. Emergency physicians have several pharmacologic agents at their disposal, including opioid and non-opioid analgesics, antipsychotics, benzodiazepines, ketamine, and combination agents. Emergency physicians should be familiar with geriatric-specific dosing, contraindications, and common adverse effects of these agents. This review article discusses the common causes and non-pharmacologic

Supervising Editor: Catherine A. Marco, MD.

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and pharmacologic management of agitation in older adults, with a specific focus on dementia, delirium, and pain.

KEYWORDS

aggression, altered mental status, delirium, dementia, emergency medicine, older adult

1 | INTRODUCTION

Agitation and aggression in older adults may be the primary reason an older adult is brought to the emergency department for medical care or may develop in response to the ED environment or underlying medical causes. The causes of agitation in older adults are multiple and can overlap, including exacerbations of behavioral and psychiatric symptoms in dementia, hyperactive delirium, manifestations of underlying psychiatric disease, and the result of alcohol or other intoxicating substances. In the coming decades, we can expect emergency physicians to care for increasing numbers of agitated older adults as the number of individuals over the age of 65 increases to nearly 98 million, constituting one-quarter of the US population by 2060.¹ Agitation is particularly common among patients with dementia,²⁻⁴ a population that is expected to double over the next 3 decades⁵ and has disproportionately higher ED utilization.⁶ To provide high-value care to these populations, emergency physicians need to understand the causes and management of agitation in older adults. The purpose of this paper is to review the key causes of agitation in older adults and provide tips for its management, with a focus on geriatric syndromes.

2 | CAUSES OF AGITATION IN OLDER ADULTS

When approaching an undifferentiated older ED patient who is agitated, aggressive, or displays features of psychosis, key considerations include determining whether the patient has a pre-existing psychiatric condition or known dementia, and obtaining collateral information regarding whether there has been an acute onset of behavioral disturbances and/or fluctuations in behavior. Less than 1% of individuals over the age of 65 have schizophrenia or schizophreniform disorders and new-onset primary psychotic disorders are exceedingly rare in older adults.^{7,8} However, up to 50% of persons living with dementia display paranoia or hallucinations⁷ and most demonstrate behavioral and psychiatric symptoms in dementia.²⁻⁴ Intoxication with alcohol is common among older adults with 9% qualifying as binge drinkers and 2% as heavy drinkers.⁹ Intoxication with alcohol and/or other substances should therefore be considered in the differential of agitation.¹⁰

2.1 | Dementia

Currently, ~5.8 million people over the age of 65 are living with Alzheimer's disease, and the prevalence of Alzheimer's disease is

expected to more than double to 13.8 million by 2050.⁵ Behavioral and psychiatric symptoms in dementias exhibited by persons living with dementia include aggression, agitation, delusions, hallucinations, anxiety, wandering, and apathy. These symptoms are estimated to impact up to 90% of people with Alzheimer's disease²⁻⁴ and behavioral and psychiatric symptoms in dementias are a defining feature of other dementias. For example, Lewy body dementia is characterized by visual hallucinations and frontotemporal dementia by behavioral disinhibition and apathy.^{4,11} Behavioral and psychiatric symptoms in dementias are more common in individuals with more advanced dementia and are associated with decline in functional abilities, increased caregiver burden, and risk for abuse and neglect.^{2,12} Up to 46% of patients with Alzheimer's disease will exhibit aggressive behaviors, including verbal abuse, threatening gestures, and physical destructiveness.¹² One-third of persons living with dementia will display aberrant motor activity, such as pacing and fidgeting.⁴ Resistance to care is also common among persons living with dementia.⁷

For caregivers of persons living with dementia who display psychotic symptoms or agitation, increased caregiver distress is associated with increased ED use, hospitalization, and healthcare-related expenditures, and caregiver distress may be the primary reason a person living with dementia presents to the ED.¹³ Alternatively, a patient may be newly agitated, aggressive, or psychotic as a result of the ED setting or due to delirium precipitated by an acute illness.^{2,7,14,15} Dementia can impact both receptive and expressive communication abilities; accordingly, anxiety, agitation, and aggressive behavior are mechanisms by which a person living with dementia may communicate pain, fear, boredom, overstimulation by the physical environment of the ED, or an unmet need such as hunger, thirst, or the need for toileting.¹⁶

2.2 | Delirium

Delirium affects between 7% and 20% of older ED patients, is independently associated with higher mortality, and, in survivors, results in accelerated functional and cognitive decline.¹⁷⁻²¹ Delirium is characterized by acute disturbances in attention, awareness, and other components of cognition that develop over a short period of time and fluctuate over the course of the day.²² There are a number of diagnostic and screening tools available for use in the ED,²³⁻²⁶ all of which include formal tests of attention as inattention is one of the defining features of delirium. Nonetheless, delirium is missed in the ED in up to 67% to 75% of cases.^{27,28} This is in part due to the short duration of time during which emergency physicians interact with patients, making it difficult

to note fluctuations in mental status. Additionally, patients who have dementia are 2- to 3-fold more likely to experience delirium in the setting of acute illness.^{14,21,29,30} In persons living with dementia, it is challenging, and at times impossible, to diagnose delirium in the ED without collateral information from a family member or caregiver about whether there has been an acute change or fluctuations in a patient's cognition.

Delirium occurs in 3 main psychomotor subtypes: hypoactive, hyperactive, and mixed. Patients with hypoactive delirium tend to be quiet, somnolent, and remain still in the bed. Patients with hyperactive delirium, which accounts for 10% of delirium among older ED patients,³⁰ may be agitated and restless, may fidget and pull covers off, or get up from their bed. Some patients with delirium have hallucinations or delusions that may be confused for a psychotic disorder or behavioral and psychiatric symptoms in dementia.³¹ The key to differentiating a primary psychotic disorder, delirium, and dementia lies in the time course of the illness. Additionally, many individuals with dementia or primary psychiatric conditions can sustain attention during formal tests of attention whereas individuals with delirium cannot.

2.3 | Primary psychiatric disorders

When assessing an older patient with agitation, primary psychiatric causes must not be overlooked. Anxiety disorders are the most prevalent psychiatric disorder among older adults, occurring at a rate of 10% in the community³² and up to 28% of older individuals in a medical setting.³³ Acute anxiety can present with signs of agitation including restlessness, pacing, irritability, and verbal agitation. Individuals with psychotic symptoms such as delusions, paranoia, hallucinations, or disorganized behavior and thought process may also be agitated. Though schizophrenia is relatively uncommon in older adults, occurring at a rate of 0.1%–0.5%, the absolute number of older adults living with schizophrenia is increasing due to improved life-expectancy and population growth.^{8,32} Mood-related psychoses, such as psychotic depression or mania, are a more common cause of psychosis in older adults in the ED, after dementia and delirium.¹⁵ Older ED patients with depression should be evaluated for suicidality, as suicide rates for men are highest among those 75 years of age or older.³⁴ In the evaluation of an agitated older ED patient, it is important to assess for primary psychiatric disorders through clinical interview, chart review, and collateral gathering, as this knowledge is critical to appropriate and effective emergency care.

3 | MANAGING AGITATION IN OLDER ADULTS

When approaching an agitated older patient, the safety of the patient, staff, other patients and visitors is paramount. When clinical circumstances dictate rapid management of the agitation, such as when the patient is at imminent risk of harm to self or others, the patient should be treated pharmacologically (described below) (Figure 1; Table 1).

When time and clinical circumstances permit, emergency physicians should try to determine whether the patient has acute delirium, dementia with behavioral and psychiatric symptoms in dementia, or a primary psychiatric condition, treat accordingly and consider non-pharmacological methods to manage agitation (described below).

3.1 | Dementia

Anxiety, agitation, and aggressive behavior may be a mechanism by which a person living with dementia expresses pain, fear, overstimulation, boredom, or unmet needs.¹⁶ The first steps in addressing mild or moderate agitation in a person living with dementia are to identify contributing factors and offer non-pharmacologic mitigation. When available, a family member or caregiver who demonstrates a calming presence should be encouraged to remain with the patient to provide reassurance and redirection and help staff understand and better manage behavioral disturbances. In older patients with cognitive impairment, traditional descriptive and numeric scales can underreport pain and lead to under-treatment. Observational methods, such as the Pain Assessment in Advanced Dementia Scale, can be used to assess for pain in patients with advanced dementia (Table 2).³⁵ In patients with concomitant vision or hearing impairment, sensory augmentation using hearing amplifiers or glasses can be offered. Patients who are bored may benefit from diversional activities, such as reading material, coloring activities, or puzzles. Functional ability and cognitive status should be considered in selecting activities. Patients with advanced dementia may have difficulty with puzzles or coloring activities but may find diversional activities such as towel folding soothing.^{16,36} Providing activities may also re-direct fidgeting behaviors, such as picking at intravenous catheters. Other inexpensive non-pharmacologic options that can mitigate fidgeting behaviors include card shuffling, fidget sensory tools, and aprons,^{36–38} as well as protective sleeves that cover the intravenous site. Sensory stimulation, including music and light therapy, may be used to ameliorate agitation in persons living with dementia and can be feasibly implemented at low cost in the ED setting^{36,37} (Figure 2), although evidence of efficacy in the ED is lacking due to absence of research.

3.2 | Delirium

Once the diagnosis of delirium is made or suspected in a patient, it is important to look for an underlying cause.^{39,40} Delirium can occur due to environmental factors, such as a new living environment or lack of visual or hearing aids, but it most often has an underlying medical cause such as dehydration, electrolyte disorders, infection, medication side effects or interactions, cardiovascular disorders, neurological problems, and trauma. The search for an underlying cause should start with a thorough history, gathering of collateral information, and a careful physical exam. The diagnostic workup should be guided by the findings on the history and physical. When the history and physical do not yield a clear cause, it is reasonable

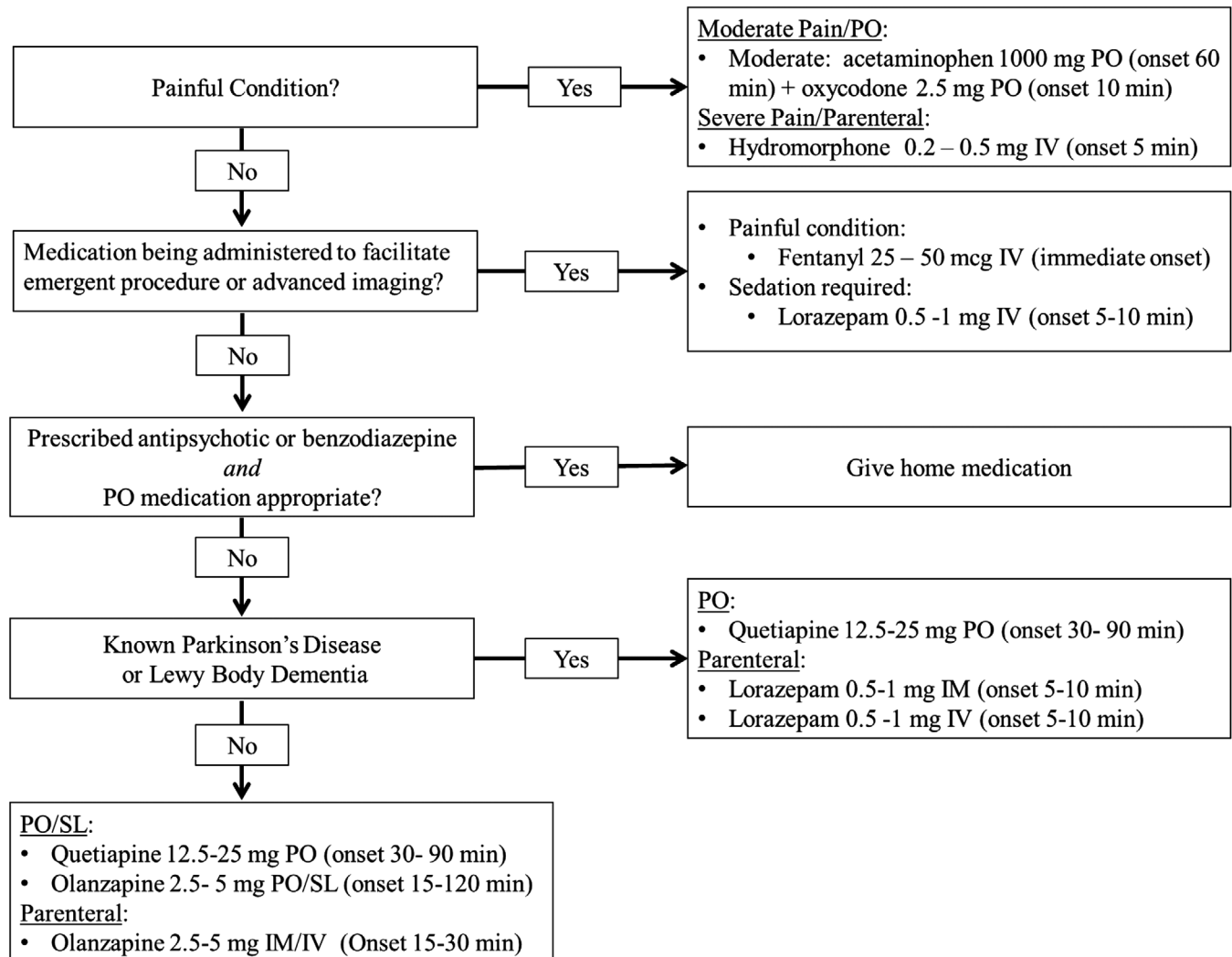


FIGURE 1 Potential framework to guide selection of pharmacologic agent to manage agitation in older emergency department patients. IM, intramuscular; IV, intravenous; PO, per os/by mouth; SL, sublingual

to cast a broad net including an electrocardiogram and laboratory tests including a complete blood count, complete metabolic panel, and urinalysis; neuroimaging should be reserved for patients with signs of trauma, focal neurologic deficit, somnolence, and/or on anticoagulation.⁴⁰

Once the precipitating causes are identified, they should be treated or managed accordingly. Other factors that may worsen delirium can also be addressed, such as pain, hunger, urinary retention, and constipation.⁴¹ By normalizing body functions, treating pain, and providing hearing and vision aids, it may be possible to prevent the worsening of delirium. Non-pharmacologic approaches, including distraction, reassurance and verbal de-escalation, are first line for managing agitated and aggressive behaviors in delirious patients.⁴⁰ Pharmacologic management of agitation should be reserved for those at immediate risk of harming themselves or others, as these medications do not improve delirium duration or severity.^{42,43} The ADEPT Tool, published by American College of Emergency Physicians, provides quick tips for the assessment, diagnosis, evaluation, prevention,

and treatment of delirium and can be easily accessed by smartphone, tablet, or computer.^{40,44}

3.3 | Primary psychiatric conditions

If other medical etiologies are ruled out and agitation is related to the exacerbation of a primary psychiatric condition, pharmacological management should be guided by the patient's existing psychiatric medication regimen or medications that have been previously effective for the patient, if known. In general, second-generation antipsychotics are preferred for patients with a primary psychotic disorder or mood disorder with psychotic features.⁴⁵⁻⁴⁸ Although benzodiazepines are generally avoided in older adults due to side effect profile, use of a low-dose short-acting benzodiazepine for the anxious agitated patient may be appropriate, particularly in patients already prescribed benzodiazepines.⁴⁹⁻⁵¹ The rapid identification and management of agitated behavior before escalation to aggression is critical to

TABLE 1 Common medications used in the treatment of pain or agitation in older adults, recommend geriatric dosing, and geriatric-specific considerations

Medication	Recommended dose and route	Time to onset (min)	Considerations and precautions in older adults
Pain			
Lidocaine 4%–5% patch	1 patch	240	<ul style="list-style-type: none"> Use for up to 12 h within a 24-h period Cut patch in half to accommodate location or deliver less drug Use a maximum of 3 patches at a time Avoid use of heat over the patch which can cause lidocaine toxicity
Acetaminophen	650–1000 mg PO	60	<ul style="list-style-type: none"> Maximum dose: 3000 mg/24 h Monitor for accumulative acetaminophen contents in OTC and prescription products
Ibuprofen	200–400 mg PO	30–60	<ul style="list-style-type: none"> Caution in patients taking blood thinners or have a history of gastrointestinal bleed ADEs: gastrointestinal hemorrhage, renal dysfunction
Morphine	5–7.5 mg PO 2–4 mg IV	30–60 5–10	<ul style="list-style-type: none"> Accumulation in renal dysfunction Potential for hypotension, flushing, urticaria, or pruritus due to histamine release Neuro-excitatory metabolites may cause CNS depression ADEs: sedation, respiratory depression, constipation, delirium
Fentanyl	25–50 mcg IV	Immediate	<ul style="list-style-type: none"> Rapid onset, highest potency Accumulation in hepatic dysfunction, preferred in renal dysfunction ADEs: sedation, respiratory depression, constipation, delirium
Hydromorphone	1–2 mg PO 0.2–0.5 mg IV	15–30 5	<ul style="list-style-type: none"> Preferred in renal dysfunction ADEs: sedation, respiratory depression, constipation, delirium
Oxycodone	2.5 mg PO	10–15	<ul style="list-style-type: none"> ADEs: sedation, respiratory depression, constipation, delirium
Agitation			
Droperidol	5 mg IM	5–10	<ul style="list-style-type: none"> Rapid onset Limited data for use in geriatric patients ADEs: QT prolongation, increased risk extrapyramidal side effects Avoid in Parkinson's disease and Lewy body dementia
Haloperidol	1–2 mg PO 1–2.5 mg IM 0.5–1 mg IV ^a	90–120 20–60 5–10	<ul style="list-style-type: none"> Rapid onset ADEs: QT prolongation, increased risk extrapyramidal side effects Avoid in Parkinson's disease and Lewy body dementia
Risperidone	0.25–1 mg PO	30–120	<ul style="list-style-type: none"> Greater efficacy in outpatient management of BPSD ADEs: orthostatic hypotension, increased risk of falls
Ziprasidone	10–20 mg IM	15–30	<ul style="list-style-type: none"> ADEs: QT prolongation, orthostatic hypotension, increased risk of falls
Olanzapine	2.5–5 mg PO/SL 2.5–5 mg IM/IV ^a	15–120 15–30	<ul style="list-style-type: none"> Available as oral disintegrating tablet Greater efficacy in outpatient management of BPSD ADEs: orthostatic hypotension, increased risk of falls Avoid IM use within 2 h of IV benzodiazepines due to risk of hypotension and cardiopulmonary depression
Quetiapine	12.5–25 mg PO	30–120	<ul style="list-style-type: none"> Greater efficacy in outpatient management of BPSD Preferred oral agent in Parkinson's disease and Lewy body dementia ADEs: high-risk of orthostatic hypotension, increased risk of falls, somnolence
Lorazepam	0.5–1 mg PO 0.5–1 mg IM 0.5–1 mg IV	10–15 5–10 5–10	<ul style="list-style-type: none"> Preferred in alcohol or benzodiazepine withdrawal May be preferred parenteral agent in Parkinson's disease and Lewy body dementia due to lack of extrapyramidal side effects Rapid onset ADEs: paradoxical excitation, may precipitate or worsen delirium Avoid IV use within 2 h of IM olanzapine due to risk of hypotension and cardiopulmonary depression

(Continues)

TABLE 1 (Continued)

Medication	Recommended dose and route	Time to onset (min)	Considerations and precautions in older adults
Midazolam	2.5–5 mg IM	10–15	<ul style="list-style-type: none"> • Rapid onset • ADEs: paradoxical excitation, may precipitate or worsen delirium • Avoid IV use within 2 h of IM olanzapine due to risk of hypotension and cardiopulmonary depression

ADE, adverse drug effects; BPSD, behavioral and psychiatric symptoms in dementia; CNS, central nervous system; IM, intramuscular; IV, intravenous; OTC, over the counter; PO, per os/by mouth; SL, sublingual.^{60,62,66,68,69,73,74,102–104}

^aIn the United States, for parenteral use haloperidol and olanzapine are FDA approved for IM administration only; IV administration of these agents is considered off-label, although may have similar safety profiles.

TABLE 2 The Pain Assessment in Advanced Dementia Scale³⁵: an observational pain scale for use in individuals with dementia

Item	Score = 0	Score = 1	Score = 2	Sum of scores
Breathing independent of vocalization	Normal	<ul style="list-style-type: none"> • Occasional labored breathing • Short period of hyperventilation 	<ul style="list-style-type: none"> • Noisy labored breathing • Long period of hyperventilation • Cheyne-stokes respirations 	
Negative vocalization	None	<ul style="list-style-type: none"> • Occasional moan or groan • Low-level of speech with a negative or disapproving quality 	<ul style="list-style-type: none"> • Repeated troubled calling out • Loud moaning or groaning • Crying 	
Facial expression	Smiling or inexpressive	<ul style="list-style-type: none"> • Sad • Frightened • Frown 	<ul style="list-style-type: none"> • Facial grimacing 	
Body language	Relaxed	<ul style="list-style-type: none"> • Tense • Distressed pacing • Fidgeting 	<ul style="list-style-type: none"> • Rigid • Fists clenched • Knees pulled up • Pulling or pushing away • Striking out 	
Consolability	No need to console	<ul style="list-style-type: none"> • Distracted or reassured by voice or touch 	<ul style="list-style-type: none"> • Unable to console, distract or reassure 	
				Total score range: 0–10

Mild pain: score 1–3; moderate pain: score 4–6; severe pain: score 7–10

ensure patient and staff safety. In cases of agitation due to decompensation of primary psychiatric disorders, consultation with emergency psychiatric providers is recommended; however, this should not delay appropriate initial pharmacologic management. If the suspicion for a primary psychiatric condition is high, but no corroborating information is available, selection of pharmacological agent may follow our algorithm for the undifferentiated patient (Figure 1).

4 | PHARMACOLOGIC MANAGEMENT OF AGITATION

There are many pharmacologic agents emergency physicians can use to manage agitation and aggression in older adults. It is important that emergency physicians understand geriatric-specific dosing of, indications for, and common adverse drug effects associated with these

agents. This article focuses on agents that are familiar to and frequently used by emergency physicians.

4.1 | Pharmacokinetic considerations

When medications are required to manage agitation in older ED patients, emergency physicians should be aware of age-related physiologic changes that impact dose selection and titration. Renal and hepatic clearance is altered by age-related decreases in organ perfusion and a decrease in number of nephrons in the kidneys, which in turn result in increased bioavailability and accumulation of certain drugs.^{52–55} Aging also causes diminished muscle mass, lower total body water, and an increase in fat content, which impact the volume of distribution for hydrophilic and lipophilic drugs.^{53,56,57} Lipophilic drugs will have a higher body distribution and lower plasma



FIGURE 2 Example of a therapeutic activity kit for patients with dementia in the emergency department or on inpatient wards³⁶ (courtesy of Jennifer Ricker and Maureen Mulligan)

concentration, resulting in a longer half-life and therapeutic duration; this includes fentanyl and most benzodiazepines and antipsychotics that are used in the ED setting. Conversely, the plasma concentration of hydrophilic drugs, including morphine, oxycodone, and hydromorphone, is higher and may lead to overmedication and toxicity.⁵⁸ Reduction of homeostatic capabilities and decline in functional reserves make geriatric patients more vulnerable to adverse drug effects, such as medication-induced postural hypotension and an associated increased risk of falls.⁵⁹ The presence of other comorbidities and polypharmacy also make older adults more vulnerable to medication side effects. Due to these aging-related changes in metabolism and distribution, one should consider the geriatric mantra of “start low and go slow” by selecting lower initial doses and slowly titrating up as needed.

4.2 | Pharmacologic approach to pain in the older adult

Older adults may become altered or agitated in the setting of pain, regardless of whether the pain is associated with an acute illness.^{14,41} Although opioids are associated with adverse drug effects when prescribed at standard doses in older adults and are considered “potentially inappropriate” in patients with history of falls or fractures,⁶⁰ under-treatment of pain can adversely impact older adults’ quality of life⁶¹ and precipitate agitation. Accordingly, if an agitated older ED patient has a painful condition, analgesics should be considered as a first step in pharmacologic management of agitation (Figure 1). Pharmacologic options for the treatment of pain in older ED patients include acetaminophen, nonsteroidal anti-inflammatory drugs

(NSAIDs), topical adjuvant agents, ketamine, and opioids. The choice of agent will be influenced by pain severity, appropriateness of oral administration, and patient factors including allergies and renal and hepatic function (Table 1). Mild pain may be preferentially treated with acetaminophen, which can be used in doses of up to 3000 mg in a 24-hour period.⁶² Moderate pain can be treated orally with a combination of scheduled acetaminophen and short-acting opioids such as hydromorphone and oxycodone at low doses. Severe pain should be treated parenterally with fast-acting opioids such as fentanyl, hydromorphone, or morphine.^{63,64} For the treatment of acute moderate to severe pain, we recommend low-dose hydromorphone in combination with scheduled acetaminophen (Figure 1) guided by an observation-based pain scale (Table 2).⁶⁴ Patient-controlled analgesia should not be used for agitated patients or patients with dementia or delirium.

Risk of adverse drug effects should be considered when selecting an agent for pain management. NSAIDs may be useful in short courses under the close supervision of primary care physicians. However, given the risks of renal dysfunction and gastrointestinal bleeding associated with NSAIDs, acetaminophen is preferred as an oral non-opioid agent. For patients who are at low risk for adverse drug effects from NSAIDs and likely to be discharged from the ED, recent evidence suggests that a single dose of ketorolac may be safe.⁶⁵ Although many opioids precipitate a release of histamine, this occurs more commonly with morphine and can result in decreased systemic vascular resistance and hypotension.⁶⁶ Additionally, morphine metabolites have neuroexcitatory properties that can accumulate in the setting of renal dysfunction and cause depression of the central nervous system.⁶⁷ The risk of side effects from metabolites is particularly important for older patients receiving hospice or palliative care who rely on frequent and

daily dosing of opioids. Because hydromorphone has inactive metabolites, it may be preferential in acute pain management.^{68,69} Meperidine should not be administered to older adults, because it may precipitate or worsen delirium.⁶⁰ Due to variable metabolism and frequent drug–drug interactions, codeine and tramadol should also be avoided in older adults.⁷⁰ Opioids should be avoided in combination with benzodiazepines and gabapentinoids; when used in combination, these drugs have the potential to cause sedation and an increase in falls.^{60,63}

4.3 | Pharmacologic approach to undifferentiated agitation in the older adult

Outside of patients with a primary psychiatric or painful condition, pharmacologic management for agitation should be limited to those demonstrating severe agitation and at risk to harm themselves or others, or to facilitate time-sensitive diagnostic imaging, procedures, or treatment.⁷¹ All currently available agents to treat agitation in older adults have notable side effects and questionable efficacy data supporting their use. In general, if pharmacologic intervention is necessary, oral therapies are preferred as they typically have fewer adverse effects and a longer therapeutic duration than intravenous or intramuscular administration. However, oral treatments have a slower onset of action and require patient cooperation. Given age-related alterations in pharmacokinetics and metabolism and the risk of polypharmacy a lower dose should be used in older adults than typically used in younger adults (Table 1).⁷² Most importantly, it is critical that emergency physicians allow adequate time for the drug to take effect. Although time of onset varies significantly by agent, average time of onset for most oral agents is at least 30 minutes, intramuscular agents at least 15 minutes, and intravenous agents 5 minutes. Droperidol and benzodiazepines are notable exceptions that have faster onset times (Table 1).^{73,74} Failing to wait for therapeutic effect may lead to dose stacking or mixing of medications, which increases the risk of adverse drug effects in the older patient.

Research into the pharmacologic management of agitation in persons living with dementia has focused on outpatient or nursing home settings and is complicated by heterogeneity in subject population, agent and dose selection, duration of treatment, and outcomes measured. Studies on the pharmacologic management of delirium, on the other hand, have predominantly been performed in the inpatient or intensive care setting. In ED studies of the pharmacologic management of acute agitation, older adults are often excluded or under-represented.^{74,75} Accordingly, recommendations have been extrapolated from non-ED based studies or prior expert consensus. ED-based investigations evaluating the safety and efficacy of pharmacologic strategies for the management of severe agitation and aggression in older adults should be prioritized for future ED research.⁷⁶

4.3.1 | Antipsychotics

First-generation antipsychotics (haloperidol and droperidol) differ from second-generation antipsychotics (clozapine, olanzapine,

risperidone, ziprasidone, quetiapine, and aripiprazole) by their mechanism of action and side effects. First-generation antipsychotics have greater activity at dopamine D₂/D₃ receptors that are highly expressed in the basal ganglia, whereas second-generation antipsychotics have a relatively potent blockade of serotonin receptors and a lesser blockade of dopamine receptors.^{77,78}

Randomized clinical trials investigating the efficacy of first-generation antipsychotics for the treatment of agitation have shown minimal improvement in behavioral scales.⁷⁹ Due to both low efficacy and a high risk of adverse effects, haloperidol is not recommended for routine use for agitation in dementia.^{71,80} Use of droperidol drastically decreased following the issuance of a black box warning by the Food and Drug Administration. As a result, there is little research into the efficacy and side effects of droperidol in management of agitation in older adults and/or patients with dementia.^{81,82} Due to dopamine receptor blockade, first-generation antipsychotics have high rates of extrapyramidal side effects such as pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia⁷⁷ and should be avoided in patients with Parkinson's disease and Lewy body dementia (Table 1; Figure 1). Although adjunctive medications such as promethazine, benztropine, or diphenhydramine are sometimes prescribed to prevent extrapyramidal side effects, these medications should not be administered to older ED patients as they are at increased risk of adverse drug effects from the anticholinergic effects, including acute delirium.⁶⁰

In large-scale outpatient studies of second-generation antipsychotics in Alzheimer's disease, olanzapine and risperidone appear to be effective in managing anger, aggression, and paranoid ideas. However, adverse effects offset the therapeutic benefit in the outpatient setting.^{83,84} Olanzapine is available in both intramuscular and oral routes that facilitates an easy transition from an intramuscular to oral agent. Quetiapine also demonstrates effectiveness on a global measure of behavioral and psychiatric symptoms in dementia in outpatient studies, but is associated with significantly higher rates of sedation.^{83,84} Of the second-generation antipsychotics, quetiapine has been shown to have the least extrapyramidal side effects and is therefore the preferred oral agent in patients with Parkinson's disease or Lewy body dementia.^{85–87} Olanzapine, risperidone, and quetiapine also antagonize histamine receptors, which results in an increased risk of orthostatic hypotension, sedation, and falls in older adults;^{88,89} the risk of orthostatic hypotension may be higher with quetiapine.⁹⁰

All antipsychotics carry a risk of QT prolongation, but this risk is greatest with first-generation antipsychotic medications and droperidol specifically has a black box warning regarding QT prolongation and risk of torsades de pointes.^{81,82} Caution should be taken in patients with channelopathies, congenital or baseline prolonged QT interval, and those who receive other QT-prolonging medications. Anecdotally, some emergency physicians co-administer intravenous magnesium sulfate when administering an antipsychotic to a patient at risk for torsades de pointes hoping to ameliorate this risk, although this is not evidence-based. First- and second-generation antipsychotics also carry a black box warning for an increased risk of mortality in elderly patients with dementia due to cardiac and infectious causes.^{91,92} In

hospitalized older adults, first- and second-generation antipsychotics are associated with an increased risk of death or cardiopulmonary arrest.⁹³ Overall, the estimated number needed to harm for commonly administered antipsychotics ranges from 26–50, so these medications should only be used when clinically necessary.⁹⁴

4.3.2 | Benzodiazepines

Benzodiazepines are first line for the treatment of patients with alcohol or benzodiazepine withdrawal or dependence (Figure 1).⁴⁵ Because benzodiazepines do not cause dopamine receptor blockade and associated extrapyramidal side effects, they may be preferable to antipsychotics in individuals with Parkinson's disease and Lewy body dementia who require parenteral treatment of severe agitation. Benzodiazepines may also be preferable to antipsychotics in patients who require sedation for emergent imaging or procedures, such as magnetic resonance imaging (MRI) or a lumbar puncture, because antipsychotics are less sedating and may require repeat administration and dose stacking to achieve the same level of sedation. If benzodiazepines are deemed the most appropriate therapy, short-acting agents such as lorazepam and midazolam should be used instead of long-acting agents such as diazepam. Otherwise, benzodiazepines should be avoided whenever possible due to their propensity to cause prolonged sedation, respiratory depression, delirium, and falls.^{60,95}

4.3.3 | Ketamine and combination agents

Ketamine is being used increasingly in the ED for acute pain and management of excited delirium syndrome among younger patients but there is minimal research evaluating its efficacy and adverse drug effects in older adults. Studies of ketamine at sub-dissociative doses for pain have demonstrated a high rate of side effects in older adults including unreality and agitation.^{96,97} Therefore, we do not currently recommend ketamine for the management of agitation in older adults. Although administering combinations of agents (eg, a "B52" combination of benzodiazepines, antipsychotics, and anticholinergics) is a common practice when treating severe agitation in younger patients, these combinations should be avoided in the geriatric population due to an increased risk of adverse drug effects.^{60,98} Intramuscular olanzapine and intravenous benzodiazepines should not be administered within 2 hours of each other due to potential risks of hypotension and cardiopulmonary depression.^{88,99}

5 | PREVENTION

Many of the non-pharmacologic strategies previously discussed can be helpful in preventing agitation and delirium in older adults. This includes encouraging a family member or caregiver to remain at bedside of a person living with dementia for reassurance and re-orientation, pain management, and providing diversional activities, vision and hear-

ing aids, hydration and nutrition.¹⁰⁰ Additional components of non-pharmacologic delirium prevention programs that can be integrated into ED care include sleep enhancement, avoiding tethers such as Foley catheters, and avoiding delirium-precipitating medications.¹⁰⁰ With respect to sleep hygiene, whenever feasible at-risk patients should not be placed in the hallways overnight. For patients in ED observation units, nighttime disruptions can be minimized by limiting nighttime vital signs, phlebotomy, and medication administration. Emergency physicians should avoid administering medications known to precipitate delirium in at-risk patients including benzodiazepines, other sedative-hypnotics, and medications with strong anticholinergics effects, such as first-generation antihistamines and muscle relaxants.⁶⁰ The American Geriatrics Society Updated Beers Criteria has a comprehensive list of medications that may be inappropriate in older adults including those that precipitate delirium.⁶⁰ There are no medications that have been consistently shown to prevent delirium.¹⁰⁰ Because prolonged ED length of stay may be associated with an increase in incident delirium in hospitalized patients, emergency physicians should minimize ED length of stay and boarding for those patients at greatest risk of developing delirium, including persons living with dementia.¹⁰¹

6 | CONCLUSION

Over the next several decades, emergency physicians will care for increasing numbers of agitated older adults due to population growth among individuals over the age of 65 and those living with dementia. Agitation and aggression may be due to hyperactive delirium, dementia, psychiatric disorders, or intoxication due to alcohol or other substances. It is critical that the physician obtain information about a patient's pre-existing psychiatric conditions, baseline cognitive status, and the acuity of any change in cognition or behavior to identify the underlying etiology. Agitation, aggression, and aberrant motor activity are common in persons living with dementia and may be how a person living with dementia communicates pain, unmet physical needs, or boredom. Non-pharmacologic approaches to manage mild or moderate agitation in persons living with dementia include diversional activities and sensory stimulation which can be easily implemented in the ED setting. New-onset psychotic symptoms in the absence of dementia should raise concern for acute delirium, and treatment should focus on identifying and managing the precipitating causes. If an agitated older ED patient has a painful condition, analgesics should be considered as a first step in the pharmacologic management of agitation. Outside of patients with primary psychiatric or painful conditions, pharmacologic management for agitation should be limited to those demonstrating severe agitation and at risk of harming themselves or others, or to facilitate time-sensitive diagnostic imaging, procedures, or treatment. Low doses of second-generation antipsychotics are preferred for the treatment of agitation in patients who do not have Parkinson's disease or Lewy body dementia. Slow titrations of medications should be employed to avoid dose stacking, drug accumulation, and side effects. Even with appropriate dosing and titration, many medications used to treat agitation carry significant risks and are associated with an

increased risk of death in hospitalized older adults. ED-based investigations evaluating the safety and efficacy of non-pharmacologic and pharmacologic strategies for the management of agitation and aggression in older ED patients should be prioritized for future research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Kennedy M, Koehl J, Shenvi CL, et al. The agitated older adult in the emergency department: a narrative review of common causes and management strategies. *JACEP Open*. 2020;1:812-823.
<https://doi.org/10.1002/emp2.12110>