Drug-associated delirium: basic pharmacologic principles and clinical considerations. A narrative review

Phat H. Le,[1] William C. Upshaw,[2] Tyler A. Le,[1] Horace Townsend,[1] Thanh P. D. Vu,[1] Jill M. Salonga,[1] Taylor Moss,[3] Sridhar Tirumala,[3] Sahar Shekoohi,[3] Adam M. Kaye,[4] Alan D. Kaye[5]

[1]School of Medicine, American University of the Caribbean, Miramar, FL; [2]School of Medicine, Louisiana State University Health Sciences Center at Shreveport, Shreveport LA; [3]Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport LA; [4]Clinical Professor of Pharmacy, Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA; [5]Professor, Vice Chairman of Research, Pain Fellowship Director, Departments of Anesthesiology and Pharmacology, Toxicology, and Neurosciences, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA, USA

ABSTRACT

Delirium is an acute state of impaired awareness and cognition with significant implications for patient outcomes, particularly in the elderly. Its clinical features include fluctuating consciousness, disorientation, hallucinations, agitation, psychomotor changes, and speech disturbances. While delirium has a broad differential diagnosis—including dementia, acute intoxication, metabolic encephalopathies, infections, and withdrawal syndromes-drug-induced delirium warrants specific attention due to its high prevalence and reversible nature. Certain drug classes are commonly associated with delirium, including anticholinergics, benzodiazepines, opioids, corticosteroids, and anticonvulsants. These drugs precipitate delirium through mechanisms such as disrupting neurotransmitter systems, including acetylcholine, dopamine, and serotonin pathways. For instance, anticholinergics impair cognition by blocking acetylcholine, while benzodiazepines and opioids can induce sedation and confusion, especially in vulnerable populations. The pathophysiology of drug-induced delirium is multifactorial, involving neurotransmitter disruptions, inflammation, and metabolic disturbances. Preventing and managing drug-induced delirium requires a detailed review of a patient's medication list, with a focus on minimizing high-risk drugs, identifying vulnerable patients (e.g., the elderly or those with polypharmacy), and monitoring for early symptoms. Treatment of delirium includes pharmacological and non-pharmacological strategies. Antipsychotics, such as haloperidol or atypical agents, are the primary pharmacological treatment, while non-pharmacological approaches involve environmental modifications, such as creating a calm, well-lit setting and involving family members for reassurance. Early recognition and prompt identification of the underlying cause are essential to improving outcomes.

Correspondence: Sahar Shekoohi, Ph.D., Assistant Professor, Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport LA 71103, USA.
E-mail: sahar.shekoohi@lsuhs.edu

Key words: BEERs criteria; drug-induced delirium; anticholinergic; antimuscarinic; adverse drug reaction.

Contributions: all authors contributed equally, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this article.

Received: 25 September 2024.
Accepted: 3 February 2025.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2025
Licensee PAGEPress, Italy
Advancements in Health Research 2025; 2:28
doi: 10.4081/ahr.2025.28

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial International License (CC BY-NC 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Introduction

Delirium is a clinical syndrome in which patients experience severe changes in cognition, attention, and level of arousal.[1] It typically develops rapidly and may be caused by different triggers, such as surgery, medications, psychological stress, and other medical illnesses.[2] Delirium can also be triggered by extreme stress, such as after a traumatic accident, as stressful events can alter the level of acetylcholine in the brain, leading to changes in brain functioning and critical cognitive processes.[3]

Delirium produces disturbances in cognition, behavior, attention, and awareness. These disturbances can manifest as cognitive impairments in memory, orientation, language, and perception, along with reduced abilities to interact with others. The potential for delirium to cause serious changes in mental abilities is often described as confused thinking and a lack of awareness of one's surroundings. Most episodes of delirium last for several days; however, some may persist significantly longer.[4] Delirium is most

commonly seen in elderly patients, with up to 20% of these individuals experiencing episodes after undergoing major surgery.[5] Risk factors associated with the development of delirium include advanced age, dementia, alcohol use, poor nutritional status, and cerebral atrophy.[6-8] Patients presenting with delirium typically exhibit several symptoms, such as disorientation to time and place, speech impairment, psychomotor abnormalities characterized by hyperactivity or hypoactivity, and sleep disturbances.[9,10]

While the pathogenesis of delirium is still not completely understood, several pathophysiological changes have been identified as contributing to its development. These include reduced activity of acetylcholine in the brain and increased activity of dopamine.[11,12] Drug-induced delirium, a subset of delirium, often arises due to pharmacologic interactions that alter neurotransmitter levels, particularly through anticholinergic or dopaminergic mechanisms. For instance, medications with strong anticholinergic properties can exacerbate acetylcholine deficiency, a critical factor in delirium development. Benzodiazepines, opioids, and corticosteroids are also implicated, as they can disrupt normal neurotransmitter balance and neural signaling, leading to acute cognitive and behavioral disturbances. Recent research highlights the role of polypharmacy in drug-induced delirium, particularly in older adults, as a significant contributor to this condition. Polypharmacy increases the risk of adverse drug interactions and cumulative anticholinergic burden, further disrupting neurotransmitter homeostasis.[13] Additionally, genetic predispositions and variations in drug metabolism, such as cytochrome P450 enzyme activity, have been identified as key factors influencing individual susceptibility to drug-induced delirium. For example, polymorphisms in cytochrome P450 enzymes may lead to altered drug clearance, resulting in higher plasma levels of certain medications and an increased risk of toxicity.[14]

Understanding these pharmacologic principles is essential for identifying at-risk patients and tailoring therapeutic strategies to prevent or manage drug-induced delirium effectively. Treatment involves addressing the underlying trigger of the condition, discontinuing or adjusting implicated medications, and providing supportive care until the patient is no longer in a delirious state.[15]

This narrative review explores the epidemiology, pathophysiology, clinical management, and prevention strategies for drug-associated delirium, with an emphasis on identifying high-risk medications and understanding their mechanisms of action.

Methods

The sources for this review are as follows: searching on PubMed, Google Scholar, Medline, and ScienceDirect using keywords Drug-induced delirium, Anticholinergic, Antimuscarinic, Adverse drug reaction, Delirium, Altered mental status, Cognitive Impairment, Delirium management. Sources were accessed between December 2023 and November 2024.

Diagnostics workup

The DSM-5 criteria provide a practical framework for assessing delirium. A change in the level of consciousness is often the first observable clue. The ability to focus, sustain, or shift attention is also often impaired and can also be assessed through testing. When delirium is suspected, formal testing should be performed by a physician.[16] Clinical assessment involves thorough history-taking, physical examination, and cognitive assessments like the Confusion Assessment Method (CAM) or the Delirium Rating Scale-Revised-98 (DRS-R-98).[17] Laboratory investigations are also generally performed, and include blood tests, imaging studies (CT or MRI scans), and electroencephalography (EEG), which aid in identifying potential underlying causes such as infections, metabolic disturbances, or cerebral pathologies.[18] Furthermore, attention to medication review is crucial, as drug-induced delirium remains a significant contributor. Recognizing and addressing reversible factors, like infections or medication toxicity, is paramount for effective management.[19,20]

Signs and symptoms

Patients with delirium often display numerous different symptoms due to their altered mental state. However, most often, patients with delirium also have other underlying conditions, thus making the diagnosis of delirium challenging. Given its severe nature, it is crucial to recognize the symptoms of delirium and promptly identify the underlying cause so that treatment can be initiated. Signs and symptoms of delirium that can be used to help make the diagnose include.[21]

1. Fluctuating consciousness: Altered levels of awareness, ranging from hyper-alertness to lethargy.
2. Disorientation: confusion regarding time, place, or person.
3. Attention issues: Difficulty focusing, sustaining, or shifting attention.
4. Hallucinations: perceiving things that are not present in reality.
5. Agitation or restlessness: increased agitation, restlessness, or irritability.
6. Sleep-wake cycle disturbance: disrupted sleep patterns, with confusion worse at night (sun downing).
7. Psychomotor changes: either slowed or hyperactive movements and behaviors.
8. Speech changes: incoherent speech or inability to organize thoughts and communicate effectively.

These symptoms often occur abruptly and can fluctuate in severity throughout the day.[17,18,22]

Risk factors

Delirium transcends its mere occurrence in the geriatric population to become a significant public health concern. With prevalence rates reaching 29-64% in hospitalized older adults and 75% in intensive care units, delirium poses a major threat to the well-being and functional independence of older individuals.[23]

Understanding the multifaceted nature of delirium in elderly patients is crucial for effective management. Four key risk factors synergistically contribute to its development: advanced age, hospitalization, anesthesia, and comorbidities. Advanced age acts as a primary predisposing factor for delirium. Physiological changes associated with aging, such as declines in neurotransmitter function, cerebral blood flow, and sensory processing, render the brain more susceptible to insults that trigger delirium. Additionally, pre-existing cognitive decline, a frequent companion of aging, further weakens the cognitive reserve, setting the stage for delirium onset.[23]

The hospital environment may also unleash a cascade of delirium-inducing factors. Sensory deprivation, unfamiliar routines, sleep disruption, and social isolation all conspire to disorient and confuse older adults, increasing their vulnerability to delirium.[24]

Furthermore, iatrogenic factors, such as the administration of certain medications may further cloud cognitive function and precipitate delirium.[25]

Anesthesia, while crucial for pain management during surgery, also carries a significant risk of delirium in older adults. The physiological stress and neurotransmitter imbalances induced by some anesthetics, coupled with pre-existing cognitive vulnerability, can significantly increase the risk of delirium post-surgery.[26] This risk further escalates with the increasing length and complexity of surgical procedures, highlighting the need for tailored anesthetic approaches and comprehensive preoperative interventions for at-risk individuals.

The presence of chronic medical conditions adds another layer of complexity to the risk profile for delirium. Neurological conditions, such as dementia and Parkinson's disease, increase vulnerability through pre-existing cognitive impairment and neurotransmitter imbalances. Chronic respiratory diseases can deprive the brain of oxygen, triggering delirium onset.[27] Pain, which is frequently associated with many medical conditions, can disrupt sleep patterns and exacerbate delirium.[27] Furthermore, the polypharmacy often employed in managing multiple chronic conditions introduces the risk of drug interactions and adverse effects, potentially mimicking or worsening delirium symptoms.[28]

Etiology and pathogenesis of drug associated delirium

Drug-induced delirium is a significant clinical concern, as various classes of medications have been implicated in its development. This phenomenon is largely due to alterations in neurotransmitter levels, particularly involving acetylcholine and dopamine.[15] Medications with strong anticholinergic properties are frequently associated with delirium, as they inhibit central cholinergic activity, which plays a crucial role in cognitive function. Drugs such as tricyclic antidepressants, paroxetine, first-generation antihistamines (e.g., diphenhydramine, hydroxyzine), trihexyphenidyl, and disopyramide have been identified as high-risk agents due to their anticholinergic burden.[15,29] The American Geriatrics Society regularly updates the BEERs criteria, a guideline identifying potentially inappropriate medications for older adults. The 2023 BEERs list highlights the increased risk of anticholinergic drugs, including scopolamine, particularly when used in combination with other medications that amplify their effects, thereby exacerbating the risk of delirium.[2,30]

Benzodiazepines represent another class of drugs commonly associated with drug-induced delirium. These agents act as positive allosteric modulators of gamma-aminobutyric acid (GABA) receptors, leading to central nervous system depression.[31,32] Elderly individuals are particularly vulnerable to benzodiazepine-induced delirium due to increased drug accumulation in adipose tissue and heightened sensitivity of GABA receptors with age.[33,34] Long-acting benzodiazepines, such as diazepam and chlordiazepoxide, carry an even greater risk due to prolonged half-lives and active metabolites.[35]

Opioids, particularly meperidine, are also strongly associated with delirium. Meperidine is metabolized into normeperidine, a neurotoxic metabolite with anticholinergic properties capable of crossing the blood-brain barrier and inducing cognitive dysfunction.[15] High-dose opioid therapy in general has been linked to delirium due to excessive opioid receptor activation, leading to dysregulation of neurotransmitter pathways.[15] Given these risks, it is recommended to avoid meperidine in elderly patients and to carefully monitor opioid use, particularly in those with preexisting cognitive impairment.[8]

Corticosteroids, tricyclic antidepressants, and traditional high-dose neuroleptics also contribute to drug-induced delirium, particularly in older adults.[35] The underlying pathogenesis of delirium related to these drugs is believed to involve complex neurotransmitter disruptions, including dopaminergic hyperactivity and cholinergic deficiency. Research suggests that a strong inhibition of postsynaptic type 1 muscarinic receptors plays a central role in the development of drug-induced delirium, which explains why clozapine, an antipsychotic with strong antimuscarinic effects, is particularly likely to induce this condition.[36] Similarly, antihistamines, which possess anticholinergic activity, have been implicated in delirium pathogenesis through their antagonism of muscarinic receptors.[36]

Recent studies have also highlighted the role of polypharmacy in increasing the risk of drug-induced delirium,[37] particularly in elderly patients. Polypharmacy leads to increased drug interactions, cumulative anticholinergic burden, and unpredictable pharmacodynamic responses.[15] Additionally, genetic variations in drug metabolism, such as polymorphisms in cytochrome P450 enzymes,[38] can affect individual susceptibility to drug-induced delirium by altering drug clearance and increasing the likelihood of toxic plasma levels.[38]

Due to the high risk of morbidity associated with drug-induced delirium, it is crucial for clinicians to conduct thorough medication reviews in at-risk patients. Identification and discontinuation of causative agents, dose adjustments, and supportive care are key strategies in mitigating this condition. High-risk individuals, particularly elderly patients and those with preexisting cognitive impairment, should be closely monitored to prevent prolonged hospital stays and intensive care admissions due to severe delirium.[35]

Differential diagnoses

Distinguishing delirium from other conditions presenting with altered mental status is imperative. Differential diagnoses include various conditions, such as dementia, acute intoxication, primary psychiatric disorders (e.g., schizophrenia), metabolic encephalopathies, fluid and electrolyte disturbances, drug or alcohol toxicity, infections, withdrawal from barbiturates, benzodiazepines, and neurological conditions (e.g., stroke or seizures).[18] Distinguishing features, such as the acute onset and fluctuating course of delirium, aid in differentiation (Table 1). Accurate and rapid evaluation is indispensable to ensure appropriate management and prevent potential harm arising due to misdiagnosis.[20]

Effective prevention, management, and treatment

Due to the complex interplay of these risk factors a multipronged approach to delirium management is warranted. Accurately diagnosing and managing underlying medical conditions, optimizing medication regimens, and prioritizing non-pharmacological interventions, such as maintaining hydration, managing pain, and ensuring adequate sleep, is critical.[28]

Preoperative considerations and tailored anesthetic approaches for older adults undergoing surgery are crucial for minimizing anesthesia-related delirium risk.[26] Within the hospital

environment, implementing delirium screening protocols, maintaining familiar routines, promoting social interaction, and minimizing unnecessary medications play a significant role.

The most important step to prevent drug-induced delirium is to treat the underlying cause by utilizing both pharmacological and non-pharmacological measures. The most common alterable origin of delirium are medications, which should be reviewed in all delirious patients. After thorough review of the patient's medication list is conducted, a healthcare provider should seek a time-based association of the onset medication with the signs and symptoms of delirium. In addition, healthcare providers should inquire about illicit drug usage, alcohol usage, and over the counter medications.[15] In patients with renal disease or kidney damage, creatinine clearance should be regularly monitored, and medications that are more disposed to causing delirium should be altered. Prescriptions with anticholinergic properties should be evaded, minimized, or exchanged with a lower anticholinergic potency. Additionally, patients diagnosed with Parkinson's disease should have their anti-parkinsonian medication adjusted to avert or treat delirium.[42] It is important for clinicians to evaluate the risk versus benefit of medications contributing to delirium, but prescriptions that are suspected of inducing delirium should be discontinued.[15]

Once delirium is diagnosed, the treatment of delirium includes

Table 1. Drug risk profiles.[37-41]

Drug class	Drug examples	Risk level	Exceptions	Risk factors
Pure anticholinergics	Atropine Benztropine Oxybutynin	High	Decreased risk if drug is less able to cross blood-brain barrier	Advanced age, dementia, polypharmacy, baseline cognitive impairment, frailty
Antidepressants	Amitriptyline Nortriptyline Paroxetine	High	MAO-A inhibitor Moclobemide is low-risk	Older age, history of depression, preexisting cognitive dysfunction, polypharmacy
Antipsychotics	Thioridazine Chlorpromazine	High	Risperidone and Clozapine are low-risk	Parkinson's disease, Lewy body dementia, baseline cognitive impairment, advanced age
Lithium	-	High	-	Renal dysfunction, dehydration, older age, polypharmacy
Anxiolytics	Lorazepam Diazepam	Moderate	Clomethiazole is low-risk	Older age, history of anxiety, respiratory disorders, prolonged sedation risk
Sedatives	Promethazine	Moderate	-	Older adults, frailty, baseline cognitive dysfunction, polypharmacy
Dopamine agonists	Ropinirole Pramipexole	Moderate	-	Parkinson's disease, history of psychosis, older age
Antiepileptics	Valproate Lamotrigine Levetiracetam	Moderate	-	History of epilepsy, hepatic dysfunction, older age, multiple drug interactions
Histamine H1 receptor blockers	Diphenhydramine Chlorpheniramine Meclizine	Moderate	-	Older adults, cognitive decline, polypharmacy, strong anticholinergic effects
Histamine H2 receptor blockers	Cimetidine Ranitidine Famotidine	Moderate	-	Renal impairment, older age, polypharmacy
Analgesics	Codeine Meperidine	Moderate	Paracetamol is low-risk	Older age, opioid-naïve patients, history of substance use disorder, respiratory disease
Antiarrhythmic	Disopyramide Verapamil Quinidine Propranolol	Moderate	-	Cardiac disease, electrolyte imbalances, older age
Diuretics	Hydrochlorothiazide Acetazolamide	Moderate	-	Dehydration risk, electrolyte imbalance, older adults
Digitalis	-	Moderate	Mainly at high concentrations	Kidney impairment, older age, narrow therapeutic index
Asthma drugs	Cortisone Theophylline	Moderate	-	Older adults, high doses, history of anxiety or agitation
Antibiotics	Ciprofloxacin Azithromycin Levofloxacin	Low	Unclear if delirium is adverse effect of drug vs. caused by infection	Underlying infection, renal dysfunction, history of delirium
Laxatives	Docusate Senna Bisacodyl	Low	-	Dehydration, frail elderly, prolonged use

pharmacological management and supportive therapy. Antipsychotics are the treatment of choice for delirium, particularly for managing agitation, hallucinations, and severe psychosis associated with the condition. Both first-generation antipsychotics (e.g., haloperidol) and second-generation antipsychotics (e.g., quetiapine, olanzapine) have been used in the management of delirium, with second-generation antipsychotics generally preferred due to their more favorable side effect profile, especially in elderly patients. Haloperidol, a typical antipsychotic, is commonly used in acute cases but is associated with extrapyramidal symptoms and sedation, making it less suitable for long-term management. Second-generation antipsychotics, such as quetiapine and olanzapine, are less likely to cause these side effects, although they may still carry risks such as sedation and metabolic disturbances. There is evidence supporting the efficacy of these medications in controlling symptoms of delirium, although they do not address the underlying causes. It is essential to start these medications at a low dose and carefully monitor for side effects, especially in older adults, who are more sensitive to antipsychotic medications. Non-pharmacological approaches, such as re-directional procedures or recollection prompts-including the use of calendars, clocks, and photographs - may also be used. It is best for delirious patients to be in a luminous and quiet environment, and all sensory insufficiencies should be corrected with the use of corrective lenses and hearing aids. When possible, healthcare team members and family members should reassure the patient and reinforce orientation while avoiding the use of physical restraints. Although patients with delirium may become non-compliant, it is good to bear in mind that complications with perception lead to wandering, agitation, anxiety, and frightfulness. Patients who are severely delirious should not be left unattended; therefore, these patients may benefit from a sitter for continuous observation.[13,43,44]

Conclusions

Delirium is a condition characterized by acute changes in cognition, attention, and arousal.[1] Elderly individuals are at an especially high risk of delirium developing and thus appropriate measures should be taken to ensure that delirium does not develop among this group. The causes of delirium are numerous though one of the most common factors that causes this condition is certain medications.[15] Because of this, when delirium is suspected, a medication review should be performed in an attempt to identify the underlying trigger. After the diagnosis of delirium is made, appropriate treatment should be initiated in an effort to get patients out of a delirious state as quickly as possible. It is critical this treatment is done rapidly as delirium may lead to significant negative health consequences for the patient including potentially even death if the delirium is not properly treated.[1]

References

1. Ramírez Echeverría M de L, Schoo C, Paul M. Delirium. StatPearls [Internet]. Treasure Island, StatPearls Publishing; 2024.
2. Mart MF, Williams Roberson S, Salas B, et al. Prevention and management of delirium in the intensive care unit. Semin Respir Crit Care Med 2021;42:112-26.
3. Cole MG, Bailey R, Bonnycastle M, et al. Partial and no recovery from delirium in older hospitalized adults: frequency and baseline risk factors. J Am Geriatr Soc 2015;63:2340-8.
4. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth 2020;125:492-504.
5. Velayati A, Vahdat Shariatpanahi M, Shahbazi E, et al. Association between preoperative nutritional status and postoperative delirium in individuals with coronary artery bypass graft surgery: A prospective cohort study. Nutrition 2019;66:227-32.
6. Nitchingham A, Kumar V, Shenkin S, et al. A systematic review of neuroimaging in delirium: predictors, correlates and consequences. Int J Geriatr Psychiatry 2018;33:1458-78.
7. Silver G, Traube C, Gerber LM, et al. Pediatric delirium and associated risk factors: a single-center prospective observational study. Pediatr Crit Care Med 2015;16:303-9.
8. McNicoll L, Pisani MA, Zhang Y, et al. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003;51:591-8.
9. Trzepacz PT, Teague GB, Lipowski ZJ. Delirium and other organic mental disorders in a general hospital. Gen Hosp Psychiatry 1985;7:101-6.
10. Ryan DJ, O'Regan NA, Caoimh RÓ, et al. Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013;3:e001772.
11. van der Mast RC, Fekkes D. Serotonin and amino acids: partners in delirium pathophysiology? Semin Clin Neuropsychiatry 2000;5:125-31.
12. Sadlonova M, von Arnim CAF. [Update on the diagnosis and treatment of delirium].[Article in German]. Inn Med (Heidelb) 2023;64:855-63.
13. Kalish VB, Gillham JE, Unwin BK. Delirium in older persons: Evaluation and management. Am Fam Physician. 2014;90(3):150-158.
14. Chan S-L, Lam J-C, Chan J-W, et al. Cytochrome P450 polymorphisms and susceptibility to drug-induced delirium: A case study. Clin Drug Investig 2015;35:537-43.
15. Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. Postgrad Med J 2004;80:388-93.
16. Gupta N, de Jonghe J, Schieveld J, Leonard M, Meagher D. Delirium phenomenology: what can we learn from the symptoms of delirium? J Psychosom Res 2008;65:215-22.
17. Carter GL, Dawson AH, Lopert R. Drug-induced delirium. Incidence, management and prevention. Drug Saf 1996;15: 29-301.
18. Francis J. Drug-induced delirium. CNS Drugs 1996;5: 103-14.
19. Thom RP, Levy-Carrick NC, Bui M, Silbersweig D. Delirium. Am J Psychiatry 2019;176:785-93.
20. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. Drugs Aging 1999;15:15-28.
21. Vilke GM, Bozeman WP, Dawes DM, et al. Excited delirium syndrome (ExDS): treatment options and considerations. J Forensic Leg Med 2012;19:117-21.
22. Gleason OC. Delirium. Am Fam Physician 2003;67:1027-34.
23. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49:51-22.
24. McCusker J, Cole M, Abrahamowicz M, et al. Environmental risk factors for delirium in hospitalized older people. J Am Geriatr Soc 2001;49:1327-34.
25. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA Intern Med 2015;175:512-20.
26. Safavynia SA, Arora S, Pryor KO, García PS. An update on postoperative delirium: Clinical features, neuropathogenesis,

and perioperative management. Curr Anesthesiol Rep 2018;8:252-62.
27. White N, Bazo-Alvarez JC, Koopmans M, et al. Understanding the association between pain and delirium in older hospital inpatients: systematic review and meta-analysis. Age Ageing 2024;53:afae073.
28. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;5:210-20.
29. Richelson E. Treatment of acute depression. Psychiatr Clin North Am 1993;16:461-78.
30. Karlsson I. Drugs that induce delirium. Dement Geriatr Cogn Disord 1999;10:412-5.
31. Foy A, O'Connell D, Henry D, et al. Benzodiazepine use as a cause of cognitive impairment in elderly hospital inpatients. J Gerontol A Biol Sci Med Sci 1995;50:M99-106.
32. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J 2013;13:214-23.
33. Greenblatt DJ, Shader RI, Harmatz JS. Implications of altered drug disposition in the elderly: studies of benzodiazepines. J Clin Pharmacol 1989;29:866-72.
34. Cook PJ. Benzodiazepine hypnotics in the elderly. Acta Psychiatr Scand Suppl 1986;332:149-58.
35. Gale L, McGill K, Twaddell S, et al. Hospital-treated deliberate self-poisoning patients: Drug-induced delirium and clinical outcomes. Aust N Z J Psychiatry 2022;56:154-63.
36. Friedrich ME, Grohmann R, Rabl U, et al. Incidence of drug-induced delirium during treatment with antidepressants or antipsychotics: a drug surveillance report of German-speaking countries between 1993 and 2016. Int J Neuropsychopharmacol 2022;25:556-66.
37. Fick DM, Steis MR, Waller JL, et al. Delirium superimposed on dementia: A review of the literature and evidence-based guidelines for management. J Am Geriatr Soc 2013;61:914-22.
38. Hshieh T, Yang T, Oh E, et al. Association between polypharmacy and risk of delirium in older adults: A systematic review and meta-analysis. J Clin Psychiatry 2017;78:e1-e10.
39. Reisinger M, Reininghaus EZ, Biasi JD, et al. Delirium−associated medication in people at risk: A systematic update review, meta−analyses, and GRADE−profiles. Acta Psychiatr Scand 2023;147:16-42.
40. Chyou T-Y, Nishtala PS. Identifying frequent drug combinations associated with delirium in older adults: Application of association rules method to a case−time−control design. Pharmacoepidemiol Drug Saf 2021;30:1402-10.
41. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911-22.
42. Ebersbach G, Ip CW, Klebe S, et al. Management of delirium in Parkinson's disease. J Neural Transm (Vienna) 2019;126:905-12.
43. Kalisvaart KJ, de Jonghe JF, van der Mast RC. Risk factors for delirium in intensive care patients: a systematic review. Intensive Care Med 2005;31:1227-33.
44. Grover S, Avasthi A. Clinical practice guidelines for management of delirium in elderly. Indian J Psychiatry 2018;60:S329-40.