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Drug-Induced Neurological Disorders in Elderly Patients

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ABSTRACT:

Drug-induced neurological disorders (DINDs) present a significant concern among elderly patients due to the widespread use of medications. This review delves into the epidemiology, pathophysiology, clinical significance, risk factors, identification, and management strategies of DINDs in this population. Elderly individuals are particularly susceptible to DINDs due to factors such as polypharmacy and age-related changes in drug metabolism and response. While primarily neurological conditions remain prevalent, DINDs substantially contribute to the overall burden of neurological disorders in the elderly, necessitating careful management. The pathophysiology of DINDs involves diverse mechanisms, complicating both recognition and treatment. Neurological symptoms resulting from adverse drug reactions manifest in various forms, ranging from cognitive impairments to severe neuromuscular complications, demanding thorough evaluation and vigilant monitoring. Multiple risk factors contribute to medication-related neurologic issues in the aging population, underlining the importance of awareness and preventive measures such as regular medication reassessments and interdisciplinary collaboration. Effective management of DINDs requires a systematic approach, including deprescribing potentially harmful medications and evaluating cognitive impact to enhance overall patient safety and well-being. Early identification of DINDs is paramount for timely intervention and prevention of irreversible neurological damage, emphasizing the need for vigilant surveillance and thorough clinical assessment. Overall, a comprehensive understanding of DINDs in elderly patients enables healthcare professionals to optimize clinical outcomes and improve patient care through evidence-based management strategies.

KEYWORDS: Drug- induced neurological disorders, elderly patients, adverse drug reactions, polypharmacy, cognitive impairment.

I. INTRODUCTION: Drug-induced neurological disorders in elderly individuals pose a substantial concern due to the rising use of medications in this demographic and their potential adverse effects on brain health(1). These disorders encompass a spectrum of conditions, ranging from mild cognitive impairments to severe outcomes like delirium, seizures, or movement disorders. It's imperative for healthcare providers to recognize the possibility of drug induced neurological disorders in elderly patients. This awareness can lead to more cautious prescribing habits, diligent monitoring of medication side effects, and prompt intervention upon the

emergence of any neurological symptoms. Educating both elderly patients and their caregivers about the potential neurological side effects of medications can facilitate early detection and reporting of concerning symptoms.

Several drug classes, including anticholinergics, benzodiazepines, opioids, and antipsychotics, are commonly associated with drug-induced neurological disorders in elderly patients(2). Given the aging population's increasing medication use and the vulnerability of aging brains, healthcare providers must acknowledge and address the risk of these disorders. While it's evident that the brain undergoes continuous changes throughout life, the interaction between drugs of abuse and age-related brain changes remains unclear. Nonetheless, substance abuse in older age can heighten risks and necessitate unique considerations for diagnosis and treatment.

Elderly individuals are notably vulnerable to the adverse impacts of drug-induced neurological disorders due to age-related alterations in the brain and increased exposure to medications. "Drug-induced neurological disorders" denotes unintended effects on the nervous system triggered by drugs or associated with their usage. These disorders are categorized under iatrogenic conditions, which encompass harm or injury resulting from therapeutic interventions or lapses in treatment. The term "induced" does not automatically imply a confirmed causal link between the drug and the disorder; it can impact the nervous system either directly (primary neurotoxicity) or indirectly through systemic disturbances (secondary neurotoxicity).

World Health Organization (WHO) defines several terms related to drug adverse effects, including adverse events, adverse drug reactions, and side effects. Vulnerability among the elderly to neurological complications from medication stems from various factors such as age-related alterations in drug processing and response, multimorbidity, and polypharmacy. Drug-Induced Neurological Disorders (DINDs) in this population can encompass a spectrum of severity, ranging from mild cognitive disturbances to severe, potentially life-threatening conditions like seizures or profound neuromuscular impairment.

A comprehensive understanding of DIND epidemiology, mechanisms, and clinical presentation is crucial for healthcare professionals managing pharmacological treatment in older adults. By examining drug classes implicated in DINDs, clinicians can make informed decisions to improve patient safety. Strategies such as regular medication reviews, dosage adjustments, and patient education are essential for preventing and addressing DINDs and ensuring holistic elderly patient care. Recognizing, diagnosing, and managing DINDs within the aging population aim to preserve neurological function and overall quality of life in older adults.

- I. **EPIDEMIOLOGY:** Drug-induced neurological disorders are prevalent among elderly patients due to polypharmacy, age-related pharmacokinetic and pharmacodynamic changes, and increased vulnerability to adverse drug reactions. Epidemiological studies have highlighted a growing incidence of drug-induced neurological disorders in this demographic, necessitating greater awareness and vigilance among healthcare professionals. Drug-induced neurological disorders (DIND) are often overlooked and not adequately reported, constituting a minor portion of all neurological conditions. Adverse drug reactions (ADRs) are typically disclosed to drug manufacturers and health authorities, but the frequency of reporting remains low. A meta-analysis conducted in US hospitals revealed a 6.7% occurrence of severe ADRs, with 0.32% resulting in fatalities, positioning them as the fourth leading cause of death in the US. In the UK, ADRs contributed to 6.5% of hospital admissions, with 80% directly linked to admission. Nonetheless, only a fraction of ADRs is documented, limiting their usefulness in diagnosing drug-induced neurological disorders. Clinical trial data and post marketing surveillance efforts aim to identify ADRs, but rare occurrences may go undetected due to small trial sizes and inadequate reporting rates. Examination of hospital case records suggests that a small portion of neurological disorders stem from drug-induced causes. Fatal ADRs, particularly those involving hemorrhages, represent approximately 3% of all deaths in the general population, with antithrombotic agents commonly implicated (3).

II. PREVELANCE: The occurrence of drug-induced neurological disorders in elderly patients varies depending on the specific disorder. However, generally, these disorders are less frequent than primary neurological conditions like stroke, dementia, Parkinsonism, and epilepsy. Research indicates that drug-induced neurological disorders make up a smaller portion of overall neurological disorders in the elderly population. It's important to note that stroke, dementia, Parkinsonism, and epilepsy are the most common neurological disorders among the elderly, with prevalence rates varying across different populations and regions. For example, stroke prevalence ranges from 12.55 to 33.34 per 1000 individuals aged 60 and above, while dementia ranges from 7.89 to 173 per 1000, depending on the geographic area and country. Parkinsonism and epilepsy have lower prevalence rates compared to stroke and dementia but still contribute to the overall burden of neurological disorders in the elderly population. In summary, while drug-induced neurological disorders are significant in clinical practice, they represent a smaller fraction of neurological disorders compared to primary neurological conditions in elderly patients(4).

III. PATHOMECHANISM: The pathogenesis of drug-induced neurological disorders (DINDs) encompasses diverse mechanisms, many of which remain unexplored. These mechanisms can be broadly classified into pharmacologically mediated, involving interactions with the drug's intended target or relevant receptors, and non-pharmacological, which are unrelated to these interactions. Pharmacologically mediated effects can produce anticipated or unanticipated biological outcomes, while non-pharmacological effects are independent of the drug's intended action, such as immune-mediated hypersensitivity reactions. Distinguishing between desirable and undesirable effects can be challenging, as exemplified by the sedative effect of intravenous diazepam in controlling status epilepticus. Although such transient neurological disturbances are typically minor and reversible, they may be outweighed by the therapeutic benefits of the drug. Additionally, drugs targeting non-neuronal systems can also impact the central nervous system (CNS). The various pathomechanisms of DINDs can be categorized into:

- i. Direct primary neurotoxicity
- ii. Indirect neurotoxicity resulting from drug-induced disturbances in other organs.
- iii. Predisposing factors related to the patient or the drug(3).

V. CLINICAL SIGNIFICANCE: When there's a justified concern about a connection to a drug or a conceivable mechanism for Drug-Induced Neurological Disorders (DINDs), it's important to include the drug as a potential factor in diagnosing the condition. In practice, Adverse Drug Reactions (ADRs) falling into categories A (probable) and B (possible) are given careful consideration for their role in the diagnosis.

DINDs are grouped based on different neurological systems, aiding physicians, and neurologists in identifying drug-related neurological issues. While this approach provides valuable information, it has limitations, as adverse drug reactions (ADRs) often affect multiple systems, not just the neurological one.

Assessing DINDs in patients undergoing multimodal treatment, like organ transplant recipients, presents challenges due to potential complications from the underlying disease, transplant procedure, and medications administered, including immunosuppressants and antibiotics, which can trigger neurological disorders.

Critical decisions must be made in liver and heart transplant cases, necessitating a comprehensive understanding of neurological disorder pathomechanisms and natural history. Discontinuing an immunosuppressant may not be warranted if evidence linking it to neurological complications is weak and the effects are transient.

Research on liver transplants indicates that CNS complications are most likely to occur during the pre-transplant period and surgical phase, particularly in patients with severe pre-existing medical conditions.

Furthermore, DINDs can present similarly to neurological disorders caused by other factors, necessitating careful differentiation in diagnosis and management(3).

VI. NEUROLOGIC SYMPTOMS AS ADRS: Adverse drug reactions (ADRs) can manifest with neurological symptoms, stemming from various mechanisms and a wide range of pharmaceutical agents. For instance, headaches can be an example. Here are symptoms and their potential drug-induced causes:

1. **Drop Attacks and Falls:** When investigating patients experiencing drop attacks and falls, it's crucial to consider a range of potential factors, including behavioral toxicity, dementia, movement disorders such as parkinsonism, loss of consciousness due to syncope or seizures, transient ischemic attacks, neuromuscular disorders like neuropathy and myopathy, myelopathy, cerebellar disorders, and vestibular disorders.
2. **Neurogenic Bladder:** Neurogenic bladder dysfunction can arise in patients due to certain medications, including encephalopathy, myelopathy, and autonomic neuropathy.
3. **Ataxia:** Patients displaying signs of ataxia may be affected by drug-induced causes impacting various parts of the central nervous system. These include cerebellar degeneration or hemorrhage, cerebral encephalopathy, spinal cord myelopathy with posterior column involvement, brainstem transient ischemic attacks, and frontal lobe lesions in encephalomyelitis.
4. **Vertigo and Dizziness:** Medications can induce vertigo and dizziness through various neurological and systemic disturbances. Neurological causes include vestibulotoxicity (e.g., aminoglycoside antibiotics), cerebellar dysfunction (e.g., anticonvulsants), and depression of central integrative centers (e.g., hypnotics). Systemic causes encompass hypotension, vasculitis, and hematological disorders.
5. **Dysarthria:** Dysarthria, characterized by impaired speech formation, can be influenced by medications acting on different parts of the nervous system. Examples include sedative-hypnotic drugs affecting the cerebral cortex's speech control, tricyclic antidepressants causing speech block through central anticholinergic effects, drugs like lithium and phenytoin inducing scanning speech via cerebellar effects, aminoglycoside antibiotics leading to myasthenic syndrome through neuromuscular blockade, and tardive dyskinesia due to neuroleptic therapy causing oro-facial movement disorders.
6. **Vomiting:** Nausea and vomiting, common symptoms in various neurological conditions, lack a protective function akin to vomiting triggered by stomach irritants. These symptoms involve neurological pathways, particularly the brainstem's vomiting center. Medication-induced neurological disorders linked to vomiting include raised intracranial pressure such as benign intracranial hypertension, encephalopathy, aseptic meningitis, and headache.

Some drug-induced disorders, like tardive dyskinesia, serotonin syndrome, and eosinophilia myalgia syndrome, are distinct neurological syndromes that require differentiation from naturally occurring neurological disorders(3).

VII. RISK FACTORS FOR MEDICATION-RELATED NEUROLOGICAL ISSUES IN THE AGING POPULATION

Risk factors contributing to medication-related neurological issues in the aging population encompass various elements, including the extensive use of multiple medications, alterations in metabolism and drug elimination due to aging, underlying medical conditions, and individual susceptibility to drug effects. Identifying and addressing these factors is paramount for preventing and managing such neurological issues in elderly patients. With the anticipated surge in substance abuse, encompassing both prescription medication misuse and illicit drug use among older adults, understanding the risks associated with drug-induced neurological disorders becomes increasingly crucial. The intricate interplay between drugs and their potential interactions can significantly impact neurological function, necessitating a nuanced approach to diagnosis

and treatment. Awareness of medication-taking behaviors can shed light on clinical presentations, such as chronic daily headaches stemming from analgesic overuse or dyskinesia resulting from excessive dopamine replacement therapy. In many instances, managing iatrogenic symptoms involves discontinuing the offending medication. Additionally, it's essential to acknowledge indirect mechanisms through which drugs may contribute to neurological problems, such as raising blood pressure or worsening glycemic control, thereby increasing the risk of cerebrovascular disease. Similarly, immunosuppressants may heighten susceptibility to infections, indirectly impacting neurological health. Different categories of neurological syndromes warrant thorough consideration in this context(5).

VIII. IDENTIFYING AND MANAGING DRUG-INDUCED NEUROLOGICAL SYMPTOMS IN THE ELDERLY

Age-related alterations in brain function and heightened exposure to medications render the elderly population particularly vulnerable to drug-induced neurological manifestations. These manifestations encompass cognitive decline, mood fluctuations, motor disturbances, and seizures. Vigilant awareness among healthcare providers regarding the propensity for medication-induced neurological symptoms in older individuals is paramount, necessitating active surveillance and prudent medication management to mitigate adverse outcomes. Mitigation strategies should center on reducing polypharmacy, meticulous medication oversight, accounting for age-related changes in drug metabolism and elimination, and evaluating individual susceptibility to drug effects. Regular medication reassessments and interdisciplinary communication facilitate the identification of potential drug interactions, allowing for tailored treatment adjustments. Decisions regarding medication cessation in elderly patients hinge on the likelihood of drug-induced cognitive impairment, the clinical significance of the underlying condition, and the availability of alternative treatments with lower cognitive side effects. Systematic evaluation of the cognitive impact of medication discontinuation, ideally through serial administration of concise cognitive assessments like the Folstein Mini-Mental Status Examination, is crucial. Even in the absence of cognitive decline, patients often benefit from discontinuation of medications with ambiguous indications. Typically, anticholinergic, and antipsychotic drugs are prime suspects for inducing cognitive impairment and thus should be the initial targets for discontinuation. However, in cases of delirium, immediate cessation of as many medications as feasible is often warranted, albeit potentially complicating subsequent identification of the causative agent(6). Effective management of drug-induced neurological disorders in elderly patients necessitates a systematic approach encompassing medication review, dose optimization, discontinuation of offending agents, and supportive care. Healthcare professionals must prioritize deprescribing potentially inappropriate medications, particularly those with a high risk of neurological adverse effects. Multidisciplinary collaboration between physicians, pharmacists, and geriatric specialists is essential to mitigate the burden of drug-induced neurological disorders in the elderly population.

IX. COMMON DRUGS THAT CAN LEAD TO NEUROLOGICAL DISORDERS IN ELDERLY PATIENTS INCLUDE:

1. Anticholinergics: Drugs with anticholinergic properties, found in some antihistamines, antidepressants, and bladder control medications, can cause cognitive impairment and delirium.
2. Benzodiazepines: Used for anxiety, insomnia, or agitation, these drugs can result in sedation, cognitive decline, and increased fall risk.
3. Opioids: Painkillers such as morphine, oxycodone, and fentanyl can cause sedation, dizziness, and increased risk of falls or confusion.
4. Antipsychotics: Medications often used for treating delusions, hallucinations, or severe agitation can contribute to movement disorders, sedation, and increased mortality in dementia patients.

5. Antiepileptics: Drugs used for seizure control can have side effects that include cognitive impairment, gait disturbances, and sedation.
6. Antidepressants: Selective serotonin reuptake inhibitors and tricyclic antidepressants can cause side effects ranging from mild confusion to severe delirium or hyponatremia.
7. Antiparkinsonian Drugs: These drugs may exaggerate confusion and hallucinations, especially in patients with pre-existing cognitive impairment.
8. Cardiovascular Drugs: Certain medications for heart conditions, such as dizziness or syncope, can contribute to cognitive changes, especially if they affect blood pressure regulation.

Understanding the potential neurological side effects of these medications is crucial for the management of elderly patients, as the risk of drug-induced neurological disorders becomes more significant due to age-related changes in drug metabolism and central nervous system sensitivity. Clinicians must exercise careful consideration when prescribing these medications, balancing the benefits against the potential risks(7).

X. THE IMPACT OF POLYPHARMACY ON NEUROLOGICAL HEALTH IN OLDER ADULTS:

Polypharmacy, the concurrent use of multiple medications, poses a significant risk to neurological health due to potential drug interactions and cumulative side effects. This risk is particularly heightened among elderly patients with multiple health conditions. Identifying adverse drug events (ADEs) in this population is challenging as they often manifest as common geriatric problems such as falls, delirium, seizures, and neuropathy, which can be mistaken for age-related or disease-related issues. Therefore, it is crucial for physicians to consider the possibility of medication-induced effects when assessing neurological symptoms in older patients.

In a review, they discuss various drug-related neurological manifestations such as movement disorders, falls, seizures, delirium, hypoglycemia, stroke, hyponatremia, neuropathy, myopathy, and serotonin syndrome. We also highlight key classes of medications commonly associated with these manifestations in the elderly, including dopamine receptor blockers, antithrombotics, anticholinergics, β -lactams, antidepressants, benzodiazepines, and mood stabilizers. The introduction of new therapies, particularly in areas like infectious diseases and cancer, brings about the potential for additional severe side effects and drug-drug interactions in elderly patients. Therapies such as immune checkpoint inhibitors and CAR-T cells, while offering extended survival benefits, may introduce novel adverse effects, including autoimmune diseases. However, data on the safety and efficacy of these therapies in older populations are limited. Recognizing the importance of addressing these issues, the European Medicines Agency (EMA) has implemented guidelines for drug development and information dissemination tailored to older patients since 2011. These guidelines emphasize the need for comprehensive benefit-risk assessments, consideration of medication errors, and monitoring of specific side effects in older populations throughout the drug lifecycle. In conclusion, managing polypharmacy and its associated risks in elderly patients requires vigilance, thorough assessment, and adherence to established guidelines. Continual monitoring and research efforts are essential to ensure the safe and effective use of medications, particularly with the emergence of novel therapies in aging populations(7).

XI. DISCUSSION:

The research conducted by M.J. Álvarez Soria and colleagues highlighted several factors associated with increased susceptibility to adverse events (AEs), although the study design couldn't definitively establish them as risk factors. However, it strongly suggested that individuals meeting certain criteria were more prone to experiencing AEs. These criteria included being female, around 62 years old, having long-standing neurological

comorbidities, and being on multiple medications (polypharmacy). While the study didn't conclusively identify these characteristics as risks, it recommended exercising extreme caution in such cases.

Polypharmacy and advanced age have previously been recognized as established risk factors for adverse drug reactions (ADRs) in general. Additionally, the presence of specific syndromes such as akinetic-rigid, dyskinetic, neuropsychiatric, or confusional symptoms should serve as red flags for doctors, signaling the potential involvement of pharmacological causes. This is particularly crucial in elderly patients, as their symptoms often take longer to resolve, increasing the risk of chronic illness. Therefore, physicians should be vigilant in assessing and managing medications in older patients with complex medical histories to mitigate the risk of adverse outcomes(8).

Late-onset neurological disorders often present with significant neuropsychiatric symptoms, profoundly impacting both patients and caregivers. These symptoms frequently emerge early and may signal future dementia onset in individuals with Mild Cognitive Impairment (MCI). While prodromal states for Dementia with Lewy Bodies (DLB) and Frontotemporal Dementia (FTD) require further clarification, managing psychiatric symptoms poses a considerable challenge in elderly patients with neurological disorders.

Depression is commonly linked to decreased quality of life in various neurological conditions like stroke, Parkinson's disease (PD), and dementia. Furthermore, treatment with psychotropic medications, though necessary for severe behavioral issues, can worsen quality of life or induce adverse effects. Caregivers also experience reduced quality of life when dealing with patients' behavioral disturbances.

Therapeutic options for managing neuropsychiatric symptoms in elderly patients with drug-induced neurological disorders are currently limited. While atypical antipsychotics and mood stabilizers offer promise in alleviating psychosis, agitation, and mood symptoms, concerns regarding side effects necessitate cautious prescribing. Conducting controlled clinical trials is crucial to establish suitable dosages and unique side-effect profiles for each neurological condition.

Additionally, exploring the effects of anti-dementia and disease-specific therapies on neuropsychiatric symptoms is essential. Early evidence suggests that cholinesterase inhibitors and memantine may alleviate physiological symptoms in Alzheimer's disease (AD) and another forms of dementia subtypes. However, further research focusing on behavioral changes as primary outcomes is vital for confidently assessing the neuropsychiatric impact of these treatments.

In summary, the development of both pharmacological and non-pharmacological interventions to address the neuropsychiatric burden of drug induced neurological disorders in elderly patients shows promise. These interventions have the potential to alleviate distress for both patients and caregivers, enhance quality of life, and mitigate behavior-related disabilities, thus meeting a critical need in geriatric neurology(9). Drug-induced neurological disorders in elderly patients require careful consideration of the complex interplay between age-related physiological changes, polypharmacy, and medication-related factors. A proactive approach to identification, management, and prevention is essential to optimize the safety and well-being of this vulnerable population.

XII. CONCLUSION: In conclusion, drug-induced neurological disorders pose significant challenges in the care of elderly patients, necessitating heightened awareness, early recognition, and comprehensive management strategies. Healthcare professionals must remain vigilant in assessing medication appropriateness and monitoring for potential adverse drug reactions, particularly in the context of polypharmacy and age-related physiological changes. Further research is warranted to elucidate the underlying mechanisms of drug-induced neurotoxicity in elderly patients and optimize therapeutic interventions to enhance patient safety and quality of life.

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