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COMMENTARY

Rethinking morphine for neuropathic pain in the elderly: a neuroimmune perspective on preclinical evidence and clinical caution

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Abstract

Managing neuropathic pain in older adults is a major clinical challenge. This commentary synthesizes emerging preclinical and clinical evidence on a critical concern: morphine, a cornerstone opioid analgesic, may paradoxically exacerbate neuropathic pain in the aging population. In the context of an age-related pro-inflammatory state (neuroinflammatory priming) and altered μ-opioid receptor (MOR) function, chronic morphine administration can activate glial cells (microglia and astrocytes), elevate pro-inflammatory cytokines, and induce opioid-induced hyperalgesia (OIH). This evidence challenges the traditional view of morphine as a neutral analgesic and reframes it as a potential modulator of the neuropathic pain cycle in the vulnerable aged nervous system. Consequently, a paradigm shift in clinical practice is warranted. We argue for prioritizing multimodal, non-opioid strategies (*e.g.*, gabapentinoids, SNRIs), employing extreme caution with opioid prescribing using a "start low, go slow" approach, and integrating comprehensive geriatric assessment to guide safer therapeutic decision-making for the elderly.

Keywords: Morphine, neuropathy, aging, neuroinflammation, chronic pain

Introduction

With the ongoing demographic shift towards an aging population worldwide, physicians are increasingly required to manage elderly patients [1]. Chronic pain is one of the most prevalent health issues among the elderly, and neuropathy, as a leading cause of this pain, profoundly impacts quality of life [2]. With increasing age, the risk of neurotoxicity, drug tolerance, and exacerbation of neuropathic pain changes [3]. Despite therapeutic advances, opioids—especially morphine—continue to be employed in managing severe and treatment-resistant pain [4]. However, aging is accompanied by structural and functional changes in both the peripheral and central nervous systems that can alter the response to morphine [5]. Emerging evidence indicates that morphine may contribute to the development or exacerbation of neuropathic pain via inflammatory and glial-mediated mechanisms [6]. This editorial commentary aims to synthesize evidence, comprehensively examine this complex interplay, and provide an integrated perspective from preclinical and clinical evidence to guide safer therapeutic decision-making for the aging population.

Age-related changes in the nervous system and implications for pain management

Peripheral neuropathy is common in individuals over 55, affecting approximately 3–4% of this population [7]. Both animal and human studies indicate that aging is associated with “neuroinflammatory priming,” characterized by baseline elevations of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in central and peripheral nervous systems [8, 9]. Reduced levels of neurotrophic factors and impaired blood-brain barrier function further increase the

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vulnerability of the aged nervous system [10].

Accurate pain assessment in older adults is essential but challenging, particularly in those with cognitive or sensory impairments [11]. While not all tools are specific to neuropathic pain, multidimensional evaluation remains critical. Behavioral scales such as the Face, Legs, Activity, Cry and Consolability (FLACC) scale [12] highlight the importance of observational assessment, whereas validated screening tools like DN4 or painDETECT questionnaires can aid self-reported evaluation in cognitively intact patients [11].

Age-related changes in pharmacokinetics and pharmacodynamics influence opioid exposure and response. In older adults, renal function decline reduces clearance of morphine-6-glucuronide (M6G), while plasma volume and distribution are decreased, resulting in higher tissue exposure during the initial hours post-dosing [13]. These effects are associated with increased activation of microglia and astrocytes, reflected by elevated expression of Iba1 and GFAP markers, along with increased production of pro-inflammatory cytokines [14]. While these findings provide important mechanistic insights, they originate from experimental models and therefore should not be directly extrapolated to clinical outcomes without caution. Clinical Evidence and Management Implications Pharmacokinetic Evidence in Humans: evidence from pharmacokinetic studies indicates that aging markedly decreases the volume of distribution (nearly 50% of that in younger adults) and plasma clearance of morphine. Consequently, drug concentrations in the peripheral compartment are higher, leading to enhanced tissue exposure during the first few hours post-dosing [15]. Consequently, initial morphine dosing should be individualized based on age and weight, with careful titration according to clinical response [16]. While these findings provide mechanistic insights, they cannot be directly extrapolated to humans without caution.

In clinical settings, older adults receiving opioids experience higher rates of adverse outcomes, including delirium, cognitive impairment, and falls [17, 18]. Observational studies also suggest that patients with pre-existing neuropathy on long-term opioid therapy may report higher neuropathic pain scores; however, these associations do not establish causality, highlighting the need for well-controlled clinical trials. Although animal studies support the hypothesis that morphine may enhance neuroinflammation in the presence of pre-existing neuropathic changes, definitive causal relationships in humans remain unproven, and these mechanisms should be interpreted as biologically plausible but not clinically confirmed.

Conclusions

Aging alters the neuroimmune environment and may modify responses to morphine. Animal studies suggest that morphine could amplify neuroinflammation, whereas clinical evidence primarily demonstrates associations with adverse outcomes rather than definitive causation. Given the potential for opioids to exacerbate neuropathic pain in older adults, treatment should prioritize individualized, multimodal approaches. Comprehensive geriatric assessment is essential to account for renal and hepatic function, cognition, comorbidities, fall risk, and polypharmacy, which together heighten the likelihood of adverse effects [11, 19]. When opioids such as morphine are unavoidable, a cautious "start low, go slow" strategy with close monitoring for opioid-induced hyperalgesia, cognitive impairment, and functional decline is critical [20]. Non-opioid agents, including gabapentinoids (gabapentin, pregabalin) and certain antidepressants, remain first-line therapies and may confer additional benefits for sleep and mood, which are often affected in neuropathic pain [11, 19]. However, these medications are not without risk: gabapentinoids may cause dizziness, sedation, peripheral edema, and gait instability, increasing fall risk, especially when combined with other central nervous system depressants [21]; antidepressants such as serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants can contribute to hyponatremia, orthostatic hypotension, anticholinergic effects, and cardiac conduction abnormalities [22].

Overall, the management of neuropathic pain in older adults requires a careful balance of risks and benefits, guided by individualized, multimodal strategies. Future research should focus on well-designed clinical studies to clarify translational relevance and identify predictive biomarkers.

Declarations

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