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PRACA POGLĄDOWA
REVIEW

The impact of opioids on cognitive abilities – balancing pain management and cognitive preservation: A narrative review

Wpływ opioidów na funkcje poznawcze – równoważenie leczenia bólu i ochrony funkcji poznawczych: przegląd narracyjny

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ABSTRACT

INTRODUCTION: Opioids are fundamental for managing moderate to severe pain, but their use is associated with the risk of cognitive impairment. A key clinical challenge is distinguishing the iatrogenic effects of opioids from the negative impact of inadequately controlled pain itself on cognitive functions. The aim of this review is to synthesize current knowledge on the mechanisms, clinical manifestations, and management strategies for cognitive risk during opioid therapy.

MATERIAL AND METHODS: A narrative literature review was conducted, using the databases PubMed, Scopus, and Google Scholar. The analysis included preclinical and clinical studies (observational and randomized), systematic reviews, and meta-analyses. The selection covered both foundational papers on pathophysiology and the latest publications on clinical manifestations and modern therapeutic approaches.

RESULTS: Cognitive impairments induced by opioids result from complex mechanisms, including neurotoxicity and impaired synaptic plasticity. The main clinical symptoms include deficits in attention, memory, and executive functions. The clinical picture is often complicated by confounding factors such as the pain itself, emotional stress, or polypharmacy. High-risk groups include older adults and patients with renal failure. Effective risk mitigation strategies include individualized dosing, opioid rotation, and the use of drugs with a potentially more favorable neurocognitive profile, such as tapentadol or buprenorphine.

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CONCLUSIONS: Effective pain management requires a paradigm shift – from focusing solely on analgesia to a holistic strategy that actively balances controlling pain with preserving cognitive function. Proactive cognitive monitoring and individualized pharmacotherapy are crucial for optimizing treatment outcomes and improving patients' quality of life.

KEYWORDS

opioids, cognitive functions, pain, palliative care, cognitive medicine

STRESZCZENIE

WSTĘP: Opioidy są podstawą w leczeniu bólu o nasileniu umiarkowanym do silnego, jednak ich stosowanie wiąże się z ryzykiem zaburzeń funkcji poznawczych. Kluczowym wyzwaniem klinicznym jest rozróżnienie jatrogennego działania opioidów od negatywnego wpływu niedostatecznie kontrolowanego bólu na funkcje poznawcze. Celem przeglądu jest synteza aktualnej wiedzy na temat mechanizmów, objawów klinicznych i strategii postępowania w przypadku ryzyka zaburzeń funkcji poznawczych podczas terapii opioidami.
MATERIAŁ I METODY: Przeprowadzono narracyjny przegląd literatury, korzystając z baz danych PubMed, Scopus i Google Scholar. Analiza objęła badania przedkliniczne i kliniczne (obserwacyjne i randomizowane), przeglądy systematyczne oraz metaanalizy. Dobór piśmiennictwa uwzględniał zarówno fundamentalne prace dotyczące patofizjologii, jak i najnowsze publikacje koncentrujące się na objawach klinicznych i nowoczesnych podejściach terapeutycznych.
WYNIKI: Zaburzenia poznawcze wywołane przez opioidy wynikają ze złożonych mechanizmów, w tym neurotoksyczności i upośledzonej plastyczności synaptycznej. Główne objawy kliniczne obejmują deficyty uwagi, pamięci i funkcji wykonawczych. Obraz kliniczny jest często komplikowany przez czynniki zakłócające, takie jak sam ból, stres emocjonalny czy polipragmazja. Do grup wysokiego ryzyka należą osoby w podeszłym wieku oraz pacjenci z niewydolnością nerek. Skuteczne strategie ograniczania ryzyka obejmują indywidualizację dawkowania, rotację opioidów oraz stosowanie leków o potencjalnie korzystniejszym profilu neurokognitywnym, takich jak tapentadol czy buprenorfina.
WNIOSKI: Skuteczne leczenie bólu wymaga zmiany paradygmatu – od koncentracji wyłącznie na analgezji do holistycznej strategii, która aktywnie równoważy kontrolę bólu z zachowaniem funkcji poznawczych. Proaktywne monitorowanie funkcji poznawczych oraz zindywidualizowana farmakoterapia mają podstawowe znaczenie dla optymalizacji wyników leczenia i poprawy jakości życia pacjentów.

SŁOWA KLUCZOWE

opioidy, funkcje poznawcze, ból, opieka paliatywna, medycyna kognitywna

INTRODUCTION

Palliative care is an approach that improves the quality of life of patients and their families who are facing life-threatening illnesses, by preventing and alleviating suffering through early identification and the thorough assessment and treatment of pain and other physical, psychosocial, and spiritual issues [1]. Chronic pain management is a fundamental aspect of palliative care. In 1986, the World Health Organization (WHO) introduced the analgesic ladder to guide adequate pain control in cancer patients. Although large-scale studies confirming its effectiveness are lacking, this method remains simple and effective for managing pain in 70%–80% of palliative care patients. The model involves a stepwise escalation from non-opioid analgesics to weak and then strong opioids, depending on pain severity and response to treatment [2]. Third-step opioids are the basis of pain treatment in cancer patients, and morphine has been the most commonly used drug in pain treatment for many years. Over the last 40 years, opioid use has increased in both developed and developing countries. These drugs are applied in both short- and long-term pain management. Improved life expectancy among cancer patients and some chronic disease courses underscore the essential role of opioids in long-term therapy. However, prolonged opioid use and increasing cumulative doses are associated with significant risks, including psychological and physical dependence, drug tolerance, and various adverse effects [3,4,5,6,7].

Common side effects include dizziness, nausea, vomiting, constipation, and respiratory depression. Less frequently observed adverse effects are delayed gastric emptying, hyperalgesia, immunological and hormonal dysfunctions, muscle rigidity, and myoclonus. Concerns about physical dependence and addiction may complicate prescribing decisions and, in some cases, may lead to inadequate pain control. Opioids exert their analgesic effects primarily through activation of MOR (mu-opioid receptor), KOR (kappa-opioid receptor), and DOR (delta-opioid receptor) receptors, located within the central nervous system (CNS). Additionally, they interact with other receptors influencing the serotonergic, noradrenergic,

dopaminergic, GABAergic, and glutamatergic systems, contributing to some of their CNS side effects [6,7,8,9]. Executive functions are crucial for effective daily functioning. Cognitive functions, or cognition, encompass a person's ability to process thoughts and interact with their environment [10]. They involve higher-order mental processes such as memory, learning, speech, reading comprehension, reasoning, planning, decision-making, and communication. The pathway of information processing includes stimulus perception, selective attention, working memory, and executive functioning. Cognition also covers the coordination and regulation of goal-oriented behavior [11]. In summary, "cognition is a multifaceted construct that includes learning, memory, language, executive function, attention, [and] social cognition, among other components" [12].

The impact of opioids on cognitive functions is complex and influenced by factors such as the duration of use, the dosage, individual patient risk factors, and the nature of the pain being treated. In cancer-related pain management, effective analgesia is paramount, often justifying the use of high opioid doses despite the potential for cognitive impairment. Conversely, in non--cancer pain, where therapy is typically long-term, the effects on cognition are more nuanced. Challenges in this context include the risks of addiction, cumulative side effects, and tolerance to escalating opioid dosages [3,9,13]. It is crucial to emphasize, however, that the foundation of effective pain management is a comprehensive diagnosis to identify the underlying pain mechanism. Pain is not a uniform phenomenon; it can be broadly categorized as nociceptive (e.g., somatic or visceral) and non-nociceptive, with neuropathic pain being a primary example [14]. This distinction is clinically vital, as neuropathic pain, often described by patients as burning or shooting, is frequently resistant or only partially responsive to opioid monotherapy [14,15]. Therefore, modern pain management relies on a multimodal therapeutic approach, which often includes the use of co-analgesics (adjuvant drugs) such as anticonvulsants or antidepressants [15]. Such a strategy not only improves analgesic efficacy, but may also allow for a lower opioid dosage, thereby potentially mitigating any adverse cognitive effects [15].

Considering the complex effects of opioids on the brain, a clear overview of the current evidence is needed. This narrative review synthesizes the knowledge on the pathophysiological mechanisms and clinical manifestations of opioid-induced cognitive impairment. It also outlines potential strategies to balance effective pain management with cognitive preservation. Given the aging population and the increasing use of opioids in non-cancer pain, understanding and mitigating cognitive side effects is becoming a priority in both palliative and chronic care settings.

METHODS

This article presents a comprehensive narrative review of the literature, designed to synthesize current knowledge on the impact of opioids on cognitive functions. A literature search was conducted using the databases PubMed, Scopus, and Google Scholar. The search strategy utilized a combination of keywords, including "opioids," "cognitive functions," "cognitive impairment," "pain management," and "palliative care". The selection criterion was articles published in English and Polish. The search was not restricted by publication date so as to ensure the inclusion of foundational papers, although priority was given to recent publications. Older references, published before 2015, were retained selectively when they provided seminal findings or foundational knowledge, particularly in areas such as opioid receptor biology, neurocognitive assessment tools, and early exploratory interventions. Their continued relevance is supported by frequent citation and a lack of newer suitable replacements. The literature search was designed to be comprehensive, encompassing foundational preclinical and clinical studies, high-impact systematic reviews and meta-analyses, and key clinical guidelines and narrative reviews that have shaped the understanding of the field. Editorials and single case reports were excluded, unless the latter served to illustrate a critical clinical point. This selection process resulted in a final sample of 52 sources used in the review.

RESULTS

Pathophysiological mechanisms

The MOR, DOR and KOR opioid receptors are widely distributed in brain structures involved in cognition, such as the prefrontal cortex, hippocampus, amygdala, and striatum [6,16,17]. The activation of these receptors by exogenous opioids can affect cognitive functions both transiently and chronically. Foundational preclinical and clinical research indicates that this receptor activation plays a crucial role in processes such as learning, attention, memory, and emotion regulation [8,9,18].

The prefrontal cortex is critical for executive functions, including planning, decision-making, and impulse control. Preclinical studies indicate that chronic activation of MORs in this region leads to impaired decision-making and increased impulsivity [18]. These functional deficits are linked to MOR-mediated modulation of neurotransmission, such as presynaptic inhibition of glutamate and GABA release, which reduces overall neuronal activity [19]. Furthermore, by inhibiting GABAergic interneurons, opioids disrupt dopaminergic signaling in the ventral tegmental area to

prefrontal cortex (VTA-PFC) pathway, weakening cognitive control [18,20]. Prolonged opioid exposure may also cause structural changes; findings from animal models suggest a reduction in dendritic density, while longitudinal imaging studies have revealed significant reductions in grey matter volume in the prefrontal cortex and cingulate gyrus after prolonged opioid therapy, correlating with poorer cognitive test scores [21].

The hippocampus is essential for memory consolidation and learning. Animal studies have shown that the activation of KORs in the hippocampus inhibits synaptic plasticity by reducing brain-derived neurotrophic factor (BDNF), which weakens long-term potentiation (LTP) and impairs synaptic efficiency, leading to memory consolidation deficits [22,23]. Other preclinical research has demonstrated that chronic opioid exposure, particularly to MOR and KOR agonists, negatively impacts hippocampal neurogenesis by inhibiting both the proliferation of progenitor cells and the differentiation of new neurons [18,22].

Regarding emotional regulation, foundational studies in rats have detected high concentrations of DOR mRNA and protein in the amygdala [16,17]. In these animal models, DOR activation modulates glutamatergic and GABAergic transmission, which reduces stress and anxiety responses. Research using selective DOR antagonists confirms this, showing an increase in anxiety-like behaviors in rats [16,17].

The striatum is involved in motivation and psychomotor function. Data from both animal and clinical studies show that chronic MOR stimulation in this region alters dopaminergic signaling, leading to reduced motivation and slowed movement [18,20]. While brief opioid administration increases dopamine release, long-term use induces adaptations that result in chronic dopamine depletion. For instance, rat studies with self-administered fentanyl show decreased midbrain dopamine levels and reduced motivational behaviors [24]. Similarly, clinical PET studies of chronic pain patients have correlated reduced D2 receptor availability in the striatum with decreased motivation and heightened pain perception [20].

Opioid receptors exhibit a phenomenon known as ligand-biased signaling, where different ligands binding to the same receptor can activate distinct intracellular pathways. This mechanism helps explain why various opioids produce a diverse range of effects, from analgesia to adverse outcomes such as tolerance and cognitive impairment [25].

Beyond direct neuronal effects, opioids also interact with the brain's immune system, particularly microglia. As demonstrated in experimental animal and cell model studies, opioids like morphine and its metabolites can activate Toll-like receptor 4 (TLR4) in microglia. This activation triggers pro-inflammatory signaling pathways (e.g., NF-κB) and the release of cytokines such as IL-1β and TNF-α, resulting in chronic neuroinflammation. This inflammatory state has been shown to impair synaptic function and inhibit both neuroplasticity and neurogenesis, contributing to opioid tolerance and hyperalgesia [26]. Although preclinical studies show that blocking TLR4 can reduce these effects [26] and inhibitors such as resatorvid have been studied in other inflammatory conditions [27], large-scale clinical trials confirming their efficacy for opioid-induced neuroinflammation are currently lacking [26,27]. A summary of the effects of opioids on key brain structures and their related cognitive impairments is provided in Table I.

Table I. Impact of opioids on selected brain structures and cognitive functions

Brain structure	Physiological role	Opioid receptors	Effect of opioids	Potential cognitive impairments
Prefrontal cortex	Executive functions (planning, decision-making, impulse control)	MOR	Inhibition of glutamate and GABA release, neuronal hyperpolarization, impaired dopaminergic transmission in the VTA-PFC pathway, synaptic plasticity changes	Impaired decision-making, reduced concentration, increased impulsivity
Hippocampus	Memory consolidation, learning, synaptic plasticity	MOR, DOR, KOR	Inhibition of LTP, decreased BDNF, impaired neurogenesis	Memory deficits, reduced cognitive flexibility, increased stress sensitivity
Amygdala	Emotional regulation, stress response	DOR	Modulation of GABAergic and glutamatergic transmission, dysfunction under chronic opioid use	Increased anxiety, emotional dysregulation, impaired attention and memory
Striatum	Motivation, motor control, reward system	MOR	Initial dopamine increase followed by chronic dopamine depletion, altered GABAergic transmission	Apathy, reduced motivation, impaired decision-making, slowed psychomotor activity

MOR – mu-opioid receptor; DOR – delta-opioid receptor; KOR – kappa-opioid receptor; GABA – gamma-aminobutyric acid; VTA-PFC – ventral tegmental area-prefrontal cortex; LTP – long-term potentiation; BDNF – brain-derived neurotrophic factor.

Clinical and neuropsychological findings

According to clinical reviews and systematic analyses, long-term opioid use presents a significant risk of neuropsychological disturbances [8,13]. The most commonly reported disorders include deficits in attention and concentration, psychomotor slowing, and impairments in working and episodic memory. In a cohort of individuals with opium use disorder, significant cognitive impairments were observed, particularly in working memory and information-processing speed [28]. Older individuals, particularly those with multiple comorbidities, are reported to be especially vulnerable to these neurotoxic effects [5,8].

Systematic reviews indicate that even short-term use (days to weeks) can result in noticeable cognitive deterioration, particularly in the domains of attention and information processing speed [13]. While some opioid-induced cognitive impairments may be reversible – particularly those resulting from acute reactions or improper dosage – chronic changes linked to reduced neuroplasticity, inhibited neurogenesis, or ongoing neuroinflammation are associated with long-term deterioration [8,13]. Clinical observations also note that many of these symptoms develop gradually and may be mistakenly attributed to the normal aging process or progression of the underlying disease [8].

A meta-analysis of 18 studies involving over 1,200 patients with chronic non-cancer pain found small to moderate impairment in attention (Standardized Mean Difference [SMD] = 0.38) and working memory (SMD = 0.42) associated with opioid use. They were found to be largely reversible after 4–24 weeks of discontinued opioid use [13]. However, results do vary: while lower-quality studies report cognitive decline, higher-quality trials did not find significant deficits – some even noted cognitive improvements, potentially due to better pain control [13].

A dose-dependent relationship between opioid exposure and cognitive dysfunction has been demonstrated in the EPOS study, involving 1,915 cancer patients. Those receiving ≥ 400 mg of morphine equivalents daily were 75% more likely to develop cognitive impairment compared to those on < 80 mg/day (Odds Ratio [OR] = 1.75) [29]. This finding is supported by systematic reviews which highlighted several studies demonstrating this link. For example, one study found a significant negative correlation between the daily morphine dose and information processing speed ($r = -0.45$, $p < 0.05$) [30]. To distinguish these effects from those caused by the underlying condition, it is crucial to also consider the cognitive impact of chronic pain itself, which is detailed in the following section.

Opioids with a potentially favorable neurocognitive profile

In response to the cognitive risks associated with classical opioids, research has focused on agents with alternative mechanisms of action. Tapentadol, which combines MOR agonism with norepinephrine reuptake inhibition, has been investigated for its cognitive-sparing potential. A comprehensive review confirms that tapentadol has a more favorable cognitive profile than traditional opioids such as oxycodone. The review summarizes findings from multiple clinical trials which indicate that patients treated with tapentadol exhibited less impairment on tests of attention and psychomotor function [31]. Similarly, buprenorphine, a partial MOR agonist, is recognized for its favorable safety profile, particularly in vulnerable populations such as the elderly. Its "ceiling effect" for respiratory depression is well-documented, and this partial agonism may also translate into a lower risk of severe cognitive impairment. Systematic reviews and comprehensive literature reviews confirm that buprenorphine is a safer option in patients with renal failure and in older adults, who are at higher risk for opioid-induced neurotoxicity, due to its stable metabolic profile and lower accumulation of active metabolites [32,33].

The confounding role of pain on cognition

Crucially, chronic pain itself is a powerful modulator of cognitive function. A comprehensive meta-analysis encompassing 37 studies and over 52,000 patients confirmed that chronic pain is associated with significant declines on cognitive screening tests, including the SF-36 (SMD = -1.50) and the Montreal Cognitive Assessment (SMD = -1.11) [34]. This is further supported by a large-scale cohort study (Health and Retirement Study), which demonstrated that individuals with persistent pain experienced a 9.2% faster decline in episodic memory and had an 8% higher risk of developing dementia over a ten-year period (Hazard Ratio [HR] = 1.08; 95% confidence interval [CI]: 1.00–1.18) [35]. Neurobiologically, these deficits are linked to structural and functional brain changes; neuroimaging studies reveal gray matter atrophy in the key areas of the medial prefrontal cortex and cingulate gyrus, alongside altered brain activity patterns, often described as "cognitive resource competition," where brain networks are reallocated to process pain at the expense of cognitive tasks [36]. The clinical relevance of this is highlighted by findings in oncology, where the presence of pain more than doubled the odds of self-reported cognitive deficits (OR = 2.3; 95% CI: 1.7–3.0) [37] and objective testing showed that female cancer

survivors with chronic pain performed significantly worse on emotion-based decision-making tasks (Iowa Gambling Task) than survivors without pain (mean score = 45.3 vs 58.7; $p < 0.01$) [38].

Potential interventions to mitigate cognitive effects

Several non-pharmacological and pharmacological interventions have been investigated for their potential to alleviate opioid-related cognitive impairments. In a randomized controlled trial (RCT) involving patients on methadone maintenance, a working memory training program led to significant cognitive improvements with a large effect size ($d = 0.54–0.67$) [39]. Similarly, Mindfulness-Oriented Recovery Enhancement (MORE) therapy, in another RCT, demonstrated a significant reduction in pain perception ($d = 0.64$) and opioid craving ($d = 0.77$) [40]. Another study confirmed the benefits of mindfulness-based interventions in opioid-treated patients, showing not only reduced pain intensity and sensitivity, but also statistically significant improvements in sleep quality [41]. Pharmacologically, a pilot study of donepezil in opioid-treated cancer patients showed a statistically significant reduction in sedation, measured by a 3.8-point mean change on the Epworth Sleepiness Scale ($p < 0.01$), as well as improvements in mood and alertness [42].

DISCUSSION

This literature review systematizes the evidence indicating that the impact of opioids on cognitive functions is a complex phenomenon, conditioned by both direct neurobiological mechanisms and clinical factors. The collected evidence indicates that the activation of opioid receptors in key brain structures leads to measurable deficits, particularly in executive functions and memory. Concurrently, the analysis of clinical data reveals that the final presentation of cognitive impairment is also significantly influenced by the drug dosage, duration of therapy, and, crucially, the pain process itself.

The observed clinical spectrum of cognitive impairments is directly explained by the described neurobiological mechanisms. Deficits in executive functions, such as difficulties in planning and decision-making [8,13], are strongly linked to opioid-induced dysregulation of the prefrontal cortex, where disturbances in neurotransmission and changes in synaptic plasticity occur [18,19,21]. Similarly, reported memory problems correspond with findings from animal models, which demonstrate that opioids inhibit neurogenesis and LTP in the hippocampus [18,22]. In turn, symptoms such as apathy, reduced motivation, and psychomotor slowing can be linked to chronic dopamine depletion in the striatum, resulting from the reward system adapting over time to MOR stimulation [20,24]. Moreover, the mechanism of ligand-biased signaling sheds light on why some opioids induce a greater degree of tolerance or cognitive impairment than others, depending on which intracellular pathways are preferentially activated [25]. In addition, the growing recognition of the role of neuroinflammation – mediated by TLR4 activation and microglial response – introduces a new, immune-based perspective to opioid-induced neurotoxicity, particularly in the context of chronic use [26,27]. The discussion of neuroinflammation also leads to the complex topic of opioid-induced hyperalgesia (OIH). This is a paradoxical state where opioids, meant to relieve pain, actually begin to increase a patient's pain sensitivity. Although OIH is a recognized phenomenon, there is still considerable debate about its true prevalence and importance in cancer-related pain [43]. This presents a major diagnostic challenge for clinicians. When a patient's pain worsens, is it because the disease is progressing, has the patient developed tolerance, or is it OIH? Making the right call is critical because the treatment for OIH is counterintuitive: it often requires reducing the opioid dosage, not increasing it.

A critical element of this discussion is the acknowledgment that the observed clinical picture in patients is the result of an interaction between two powerful factors: the pain itself and the action of opioids. As shown by current meta-analyses [34] and cohort studies [35], chronic pain per se is an independent risk factor for cognitive decline. The magnitude of this phenomenon is striking: it not only leads to a measurable, 9% faster decline in memory performance, but it may also slightly elevate the long-term risk of developing dementia [35].

This may reflect the structural brain changes visible in neuroimaging studies, which document atrophy in areas responsible for attention, executive control, and memory encoding – particularly the medial prefrontal cortex and cingulate gyrus – consistent with the concept of cognitive resource competition [36]. Understanding this fact is essential for the differential diagnosis of cognitive deficits, allowing clinicians to distinguish symptoms stemming from the underlying disease, which themselves can more than double the risk of cognitive impairment from the iatrogenic effects of pharmacotherapy [37]. The clinical expression of this interaction is further evidenced by objective behavioral data, such as poorer performance on decision-making tasks among patients experiencing pain [38], reinforcing the need for integrated cognitive-pain assessment. The impact of opioids on cognitive functions is not uniform and can shift over the course of treatment. While some cognitive effects in non-cancer pain can be reversible after drug discontinuation [13], the picture is complicated by the

development of tolerance. A classic clinical example is tolerance to sedation: many patients who are initially drowsy for the first few days of therapy find that this effect wears off over time. This adaptation can be beneficial for a patient's daily functioning, but it can also be misleading. The fading sedation might mask persistent, more subtle deficits in other cognitive areas (e.g., executive functions), which may not improve in the same way. This highlights a key clinical point: subjective reports of sleepiness are not a reliable measure of the overall cognitive impact of opioids, underscoring the need for objective monitoring [8]. Moreover, the dose-response relationship is well--documented. The EPOS study [29] clearly demonstrated a higher risk of cognitive impairment at higher morphine equivalent doses, a finding supported by the conclusions of systematic reviews [30]. Importantly, these findings align with longitudinal neuroimaging studies that demonstrate dose-related reductions in gray matter volume in regions critical to cognition [21], thereby providing a structural basis for the observed impairments. This contrasts with the more severe and potentially persistent impairments observed in populations with long-term, high-dose exposure, such as in opioid use disorder [28], where chronic neuroadaptive changes in the brain are more pronounced.

The clinical expression of neurotoxicity is strongly modulated by the patient's individual risk factors. The elderly are a particularly vulnerable group, in whom reduced cognitive reserve, changes in drug pharmacokinetics, and polypharmacy significantly increase susceptibility to adverse effects [44]. Organ failure, especially renal impairment, is also a key factor. In patients with impaired renal function, active, neurotoxic metabolites of certain drugs, such as morphine-3-glucuronide and morphine-6-glucuronide, can accumulate, leading to delirium and severe sedation [32]. This necessitates the individualization of therapy and the selection of opioids with a safer metabolic profile in this group, such as buprenorphine or fentanyl [32,33].

The above findings carry significant implications for daily clinical practice, underscoring the need to proactively monitor cognitive functions, rather than passively wait for patient complaints. Regular assessment, especially in at-risk patient groups, may enable the early detection of deficits when they are still reversible. For this purpose, simple screening tools such as the Montreal Cognitive Assessment [45] can be useful. In the context of pharmacotherapy, proactive strategies extend beyond symptomatic treatment to include the conscious selection and modification of the opioid regimen. Opioid rotation is a recognized clinical strategy that, by utilizing the phenomenon of incomplete cross-tolerance, can reduce the severity of adverse effects while maintaining effective analgesia [46]. Furthermore, a growing body of data suggests that opioids with alternative mechanisms of action may offer a more favorable cognitive profile. This applies to tapentadol, for example; its dual action (MOR agonism and norepinephrine reuptake inhibition) and lower μ-load result in fewer opioid-related toxicities, such as constipation and nausea, when compared to pure MOR agonists [47]. Buprenorphine is another example, whose status as a partial agonist and the resulting ceiling effect make it a safer option, particularly in the elderly and patients with renal failure [33].

In the realm of non-pharmacological interventions, RCTs provide promising evidence of the effectiveness of cognitive training [39] and mindfulness-based therapies [40,41], which show measurable improvement with a large effect size. These strategies can be complemented by regular, moderate-intensity physical activity, which supports general brain neuroplasticity [48]. Notably, these approaches may counteract the mechanisms of opioid-induced cognitive dysfunction by enhancing hippocampal neurogenesis, regulating stress response systems, and reducing systemic inflammation – thus targeting several of the identified pathophysiological pathways in parallel. Supportive pharmacological strategies are considered in cases where modifying the opioid dosage is not possible or insufficient and cognitive symptoms are significantly reducing the patient's quality of life. Particularly interesting results in this regard come from a pilot study which showed that donepezil, a cholinesterase inhibitor, effectively reduced excessive sedation in opioid-treated cancer patients. Beyond sedation, improvements in mood and alertness were noted, which may reflect more global enhancement of cholinergic tone in cortical networks implicated in attention and arousal [42]. Similar benefits in improving concentration and alleviating fatigue in cancer patients have been observed with the use of psychostimulant drugs, such as methylphenidate [49].

However, it must be emphasized that the current evidence for the efficacy of these interventions in mitigating specific, opioid-induced cognitive deficits is still limited and comes mainly from pilot studies. Their inclusion in standard-of-care protocols will require further, large-scale clinical trials [50] to confirm their safety and define optimal therapeutic protocols in this patient population. It should be noted that this paper, as a narrative review, is inherently susceptible to subjectively selected samples and does not systematically cover all available studies. Furthermore, the evidence base itself has significant limitations. Many detailed pathophysiological mechanisms, especially concerning neuroplasticity and neuroinflammation, have been elucidated primarily through animal model studies, which require caution when extrapolating the results to humans. Clinical

studies, in turn, are very heterogeneous in terms of the drugs used, the dosages, the duration of therapy, and the neuropsychological tools employed, which makes it difficult to compare results and formulate definitive recommendations. Moreover, although neuroimaging studies provide fascinating insights into structural and functional brain changes [51,52], they often focus on the specific population of individuals with opioid use disorder, which does not always fully correspond to the situation of chronic pain patients undergoing therapeutic treatment.

A future challenge is to develop integrated strategies within the dynamic field of "cognitive medicine" [10]. Further research is needed on combining standard neuropsychological tests with advanced neuroimaging techniques, to not only identify deficits but also to monitor brain neuroplasticity in response to treatment, such as opioid discontinuation or the implementation of naltrexone therapy [52]. In pharmacotherapy, instead of focusing solely on symptoms, interventions targeting the underlying pathophysiological mechanisms, such as dysregulation of the glutamatergic system [53] or chronic neuroinflammation, should be investigated. In this context, early-phase studies exploring the neuroprotective potential of TLR4 inhibitors (e.g., resatorvid) offer promising leads for addressing opioid--induced immune dysregulation [27], although their translation into human populations remains to be confirmed. Further new directions in pharmacotherapy include the development of multi-mechanistic drugs, such as those that combine MOR agonism with nociceptin/orphanin FQ peptide (NOP) receptor activation. The NOP receptor, though part of the opioid receptor superfamily, has a unique functional profile. Its activation can produce analgesia while simultaneously counteracting many of the adverse effects associated with classical MOR agonists, including respiratory depression, tolerance, and reward-related behaviors. This dual-target approach therefore represents a promising strategy to dissociate potent analgesia from life-threatening side effects, potentially offering a safer class of analgesics for the future [54]. Ultimately, this all points towards a more holistic perspective in pain management, one that is best exemplified by the management of complex pain conditions. A thorough diagnosis that identifies a specific type of pain, such as a neuropathic component, allows clinicians to move beyond simple opioid titration and introduce targeted co-analgesics. For neuropathic pain, this often means using drugs such as gabapentin or pregabalin, or antidepressants such as duloxetine. This multimodal approach has a powerful dual benefit: it is often more effective for managing complex or opioid-resistant pain, and it serves as a key strategy for cognitive preservation. By successfully treating pain with these agents, clinicians can often reduce the total daily dose of opioids, directly tackling the central challenge of this review: how to balance effective pain relief with minimizing cognitive side effects [55]. Effective pain management is the foundation of care, especially in oncology [56], and it is important to remember that cognitive problems in cancer patients can result from many factors, including the pain itself [37,38]. Furthermore, landmark research has demonstrated that early and well-conducted palliative care, which includes rational pain management, improves quality of life and may also extend survival [57]. The pursuit of a balance between providing analgesia and preserving cognitive function is therefore not a zero-sum game, but a key element of comprehensive, effective patient care.

CONCLUSIONS

Opioids are fundamental to modern pain management, yet their efficacy is challenged by the significant risk of cognitive impairment. This review underscores the fact that these cognitive deficits are not merely a pharmacological side effect, but the result of a complex interplay between the neurobiological actions of the drug and the parallel neurotoxic effects of chronic pain itself. Consequently, a paradigm shift is necessary, moving from a singular focus on analgesia to a holistic strategy that actively balances effective pain relief with preserving cognitive function. This requires an integrated approach, including individualized dosages, regular cognitive monitoring, and non-pharmacological and emerging therapeutic strategies. The pursuit of this balance is not a zero-sum game, but an essential component of comprehensive, patient-centered care, aimed at maximizing both quality of life and functional autonomy.

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Authors' contribution

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REFERENCES

1. Roth AR, Canedo AR. Introduction to Hospice and Palliative Care. Prim Care. 2019;46(3):287–302. doi: 10.1016/j.pop.2019.04.001.
2. Anekar AA, Hendrix JM, Cascella M. WHO Analgesic Ladder. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
3. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569–576. doi: 10.1097/01.j.pain.0000460357.01998.f1.
4. Krashin D, Murinova N, Jumelle P, Ballantyne J. Opioid risk assessment in palliative medicine. Expert Opin Drug Saf. 2015;14(7):1023–1033. doi: 10.1517/14740338.2015.1041915.
5. Gaertner J, Boehlke C, Simone CB 2nd, Hui D. Early palliative care and the opioid crisis: ten pragmatic steps towards a more rational use of opioids. Ann Palliat Med. 2019;8(4):490–497. doi: 10.21037/apm.2019.08.01.
6. Valentino RJ, Volkow ND. Untangling the complexity of opioid receptor function. Neuropsychopharmacology. 2018;43(13):2514–2520. doi: 10.1038/s41386-018-0225-3.
7. Jean YK, Gitlin MC, Reynolds J, Candiotti KA. Tramadol-associated hallucinations: a systematic review and narrative synthesis of their pathophysiology, diagnosis, and treatment. Can J Anaesth. 2020;67(3):360––368. doi: 10.1007/s12630-019-01548-9.
8. Dhingra L, Ahmed E, Shin J, Scharaga E, Magun M. Cognitive effects and sedation. Pain Med. 2015;16(Suppl 1):S37–S43. doi: 10.1111/pme.12912.
9. Wojtasik-Bakalarz K, Woroń J. Drug-induced delirium in ICU hospitalized patients. [Article in Polish]. Anaesthesiol Rescue Med. 2021;15:123–129. doi: 10.53139/AIR.20211513.
10. Wallin A, Kettunen P, Johansson PM, Jonsdottir IH, Nilsson C, Nilsson M, et al. Cognitive medicine – a new approach in health care science. BMC Psychiatry. 2018;18(1):42. doi: 10.1186/s12888-018-1615-0.
11. Mosiołek A. Cognitive test methods. [Article in Polish]. Psychiatr. 2014;11(4):215–221.
12. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol. 2014;10(11):634–642. doi: 10.1038/nrneurol.2014.181.
13. Akhurst J, Lovell M, Peacock A, Bruno R. A systematic review and meta-analysis of cognitive performance among people with chronic use of opioids for chronic non-cancer pain. Pain Med. 2021;22(4):979–993. doi: 10.1093/pm/pnab005.
14. Kocot-Kępska M. Ból neuropatyczny. Medycyna Praktyczna, 21.08.2020 [online] https://www.mp.pl/bol/ekspert/242537,bol-neuropatyczny [accessed on 4 August 2025].
15. Szczudlik A, Dobrogowski J, Wordliczek J, Stępień A, Krajnik M, Leppert W, et al. Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the study of pain and the Polish Neurological Society – part one. Neurol Neurochir Pol. 2014;48(4):262–271. doi: 10.1016/j.pjnns.2014.07.011.
16. Mansour A, Fox CA, Akil H, Watson SJ. Opioid-receptor mRNA expression in the rat CNS. Trends Neurosci. 1995;18(1):22–29. doi: 10.1016/0166-2236(95)93946-u.
17. Mansour A, Fox CA, Burke S, Meng F, Thompson RC, Akil H, et al. Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in situ hybridization study. J Comp Neurol. 1994;350(3):412–438. doi: 10.1002/cne.903500307.
18. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3(8):760–773. doi: 10.1016/S2215-0366(16)00104-8.
19. Reeves KC, Shah N, Muñoz B, Atwood BK. Opioid receptor-mediated regulation of neurotransmission in the brain. Front Mol Neurosci. 2022;15:919773. doi: 10.3389/fnmol.2022.919773.
20. Taylor AMW, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction. Pain. 2016;157(6):1194–1198. doi: 10.1097/j.pain.0000000000000494.
21. Schmidt A, Vogel M, Baumgartner S, Wiesbeck GA, Lang U, Borgwardt S, et al. Brain volume changes after long-term injectable opioid treatment: A longitudinal voxel-based morphometry study. Addict Biol. 2021;26(4): e12970. doi: 10.1111/adb.12970.
22. Eisch AJ, Barrot M, Schad CA, Self DW, Nestler EJ. Opiates inhibit neurogenesis in adult rat hippocampus. Proc Natl Acad Sci U S A. 2000; 97(13):7579–7584. doi: 10.1073/pnas.120552597.
23. Zhou HY, Chen SR, Chen H, Pan HL. Opioid-induced long-term potentiation in the spinal cord is a presynaptic event. J Neurosci. 2010;30(12):4460–4466. doi: 10.1523/JNEUROSCI.5857-09.2010.
24. Wang W, Xie X, Zhuang X, Huang Y, Tan T, Gangal H, et al. Striatal μ-opioid receptor activation triggers direct-pathway GABAergic plasticity and induces negative affect. Cell Rep. 2023;42(2):112089. doi: 10.1016/j.celrep.2023.112089.
25. Raehal KM, Schmid CL, Groer CE, Bohn LM. Functional selectivity at the μ-opioid receptor: implications for understanding opioid analgesia and tolerance. Pharmacol Rev. 2011;63(4):1001–1019. doi: 10.1124/pr.111.004598.
26. Green JM, Sundman MH, Chou YH. Opioid-induced microglia reactivity modulates opioid reward, analgesia, and behavior. Neurosci Biobehav Rev. 2022;135:104544. doi: 10.1016/j.neubiorev.2022.104544.
27. Kuzmich NN, Sivak KV, Chubarev VN, Porozov YB, Savateeva--Lyubimova TN, Peri F. TLR4 signaling pathway modulators as potential therapeutics in inflammation and sepsis. Vaccines. 2017;5(4):34. doi: 10.3390/vaccines5040034.
28. Sanjari Moghaddam H, Shadloo B, Shahkhah H, Tafakhori A, Haghshomar M, Meshkat S, et al. Cognitive impairment in opium use disorder. Behav Neurol. 2021;2021:5548623. doi: 10.1155/2021/5548623.
29. Kurita GP, Sjøgren P, Ekholm O, Kaasa S, Loge JH, Poviloniene I, et al. Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: a multinational study. J Clin Oncol. 2011;29(10):1297–1303. doi: 10.1200/JCO.2010.32.6884.
30. Pask S, Dell'Olio M, Murtagh FEM, Boland JW. The effects of opioids on cognition in older adults with cancer and chronic noncancer pain: A systematic review. J Pain Symptom Manage. 2020;59(4):871–893.e1. doi: 10.1016/j.jpainsymman.2019.10.022.
31. Zavaleta-Monestel E, Anchía-Alfaro A, Villalobos-Madriz J, Munich A, García-Montero J, Quesada-Villaseñor R, et al. Tapentadol: A comprehensive review of its role in pain management. Cureus. 2024;16(11):e74307. doi: 10.7759/cureus.74307.
32. Sołtysik A, Graczyk M, Woroń J. Use of opioid analgesics in chronic kidney disease. Palliat Med Pract. 2022;16(3):156–166. doi: 10.5603/PMPI.2022.0010.
33. Dalal S, Chitneni A, Berger AA, Orhurhu V, Dar B, Kramer B, et al. Buprenorphine for Chronic Pain: A Safer Alternative to Traditional Opioids. Health Psychol Res. 2021;9(1):27241. doi: 10.52965/001c.27241.
34. Zhang X, Gao R, Zhang C, Chen H, Wang R, Zhao Q, et al. Evidence for cognitive decline in chronic pain: A systematic review and meta-analysis. Front Neurosci. 2021;15:737874. doi: 10.3389/fnins.2021.737874.
35. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. JAMA Intern Med. 2017;177(8):1146–1153. doi: 10.1001/jamainternmed.2017.1622.
36. Patel M, Hasoon J, Diez Tafur R, Lo Bianco G, Abd-Elsayed A. The impact of chronic pain on cognitive function. Brain Sci. 2025;15(6):559. doi: 10.3390/brainsci15060559.
37. Jean-Pierre P, Winters PC, Ahles TA, Antoni M, Armstrong FD, Penedo F, et al. Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study. J Oncol Pract. 2012;8(1):30–34. doi: 10.1200/JOP.2011.000231.
38. Masiero M, Durosini I, Filipponi C, Campanini ML, Pravettoni G. Chronic pain in breast cancer survivors is linked with an impairment on emotion-based decisions and fatalistic time orientation. Curr Psychol. 2024;43:27680–27689. doi: 10.1007/s12144-024-06344-3.
39. Rass O, Schacht RL, Buckheit K, Johnson MW, Strain EC, Mintzer MZ. A randomized controlled trial of the effects of working memory training in methadone maintenance patients. Drug Alcohol Depend. 2015;156:38–46. doi: 10.1016/j.drugalcdep.2015.08.012.
40. Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM, Howard MO. Mindfulness-oriented recovery enhancement for chronic pain and

prescription opioid misuse: results from an early-stage randomized controlled trial. J Consult Clin Psychol. 2014;82(3):448–459. doi: 10.1037/a0035798.
41. Zgierska AE, Burzinski CA, Cox J, Kloke J, Stegner A, Cook DB, et al. Mindfulness meditation and cognitive behavioral therapy intervention reduces pain severity and sensitivity in opioid-treated chronic low back pain: pilot findings from a randomized controlled trial. Pain Med. 2016;17(10):1865––1881. doi: 10.1093/pm/pnw006.
42. Bruera E, Strasser F, Shen L, Palmer JL, Willey J, Driver LC, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage. 2003;26(5):1049–1054. doi: 10.1016/S0885-3924(03)00332-4.
43. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. Pain Med. 2015;16(Suppl 1):S32–S36. doi: 10.1111/pme.12914.
44. Rekatsina M, Paladini A, Viswanath O, Urits I, Myrcik D, Pergolizzi J, et al. Opioids in the elderly patients with cognitive impairment: a narrative review. Pain Ther. 2022;11(2):381–394. doi: 10.1007/s40122-022-00376-y.
45. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–699. doi: 10.1111/j.1532-5415.2005.53221.x.
46. Smith HS, Peppin JF. Toward a systematic approach to opioid rotation. J Pain Res. 2014;7:589–608. doi: 10.2147/JPR.S55782.
47. Boland JW. Tapentadol for the management of cancer pain in adults: an update. Curr Opin Support Palliat Care. 2023;17(2):90–97. doi: 10.1097/SPC.0000000000000641.
48. Sumińska S. The impact of physical activity on cognitive functions. [Article in Polish]. Med Pr. 2021;72(4):437–450. doi: 10.13075/mp.5893.01103.
49. Andrew BN, Guang NC, Jaafar NRN. The Use of Methylphenidate for Physical and Psychological Symptoms in Cancer Patients: A Review. Curr Drug Targets. 2018;19(8):877–887. doi: 10.2174/1389450118666170317162603.
50. Malík M, Tlustoš P. Nootropics as cognitive enhancers: types, dosage and side effects of smart drugs. Nutrients. 2022;14(16):3367. doi: 10.3390/nu14163367.
51. Atanasova N, Todeva-Radneva A, Stoyanova K, Psederska E, Stoyanov D, Traykova N, et al. Functional connectivity in resting-state fMRI (rs-fMRI) in opioid use disorder. Eur Phys J Spec Top. 2025;234(15):4127–4137. doi: 10.1140/epjs/s11734-025-01591-2.
52. Shi Z, Li X, Todaro DR, Cao W, Lynch KG, Detre JA, et al. Medial prefrontal neuroplasticity during extended-release naltrexone treatment of opioid use disorder – a longitudinal structural magnetic resonance imaging study. Transl Psychiatry. 2024;14(1):360. doi: 10.1038/s41398-024-03061-0.
53. Heinsbroek JA, De Vries TJ, Peters J. Glutamatergic Systems and Memory Mechanisms Underlying Opioid Addiction. Cold Spring Harb Perspect Med. 2021;11(3):a039602. doi: 10.1101/cshperspect.a039602.
54. Coluzzi F, Rullo L, Scerpa MS, Losapio LM, Rocco M, Billeci D, et al. Current and future therapeutic options in pain management: multi-mechanistic opioids involving both MOR and NOP receptor activation. CNS Drugs. 2022;36(6):617–632. doi: 10.1007/s40263-022-00924-2.
55. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2(6):e627. doi: 10.1097/PR9.0000000000000627.
56. Portenoy RK. Treatment of cancer pain. Lancet. 2011;377(9784):2236––2247. doi: 10.1016/S0140-6736(11)60236-5.
57. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733–742. doi: 10.1056/NEJMoa1000678.