

Cognitive impact of chronic opioid use

Impacto cognitivo del uso crónico de opioides

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ABSTRACT

Introduction: the impact of chronic opioid use has been related to a wide range of cognitive disorders, ranging from minor deficiencies in cognitive abilities to problems in abilities such as attention, learning, memory, and executive functions. **Objective:** to carry out a systematic review to research the cognitive impact in patients who use opioids chronically and to assess the severity of this impact. **Method:** randomized clinical trials, case-control studies, prospective and retrospective cohorts were evaluated in two databases: PubMed and Cochrane Central, using the following search terms: "analgesic opioids", "cognitive dysfunction", "cognition impairments", "chronic disease" and "abuse, substance". The search was in English, Spanish, and Portuguese for studies conducted in adult humans with chronic opioid use and its cognitive impact. **Results:** 7 studies were selected, 5 of which the patients used tramadol and the negative cognitive impact was verified, a study with the use of

tapentadol with a positive impact on cognition and a study with the use of hydrocodone with a positive impact on neurocognition of patients. **Conclusions:** despite the limitations found, as a conclusion it is considered that tramadol has a negative impact on neurocognition, which does not occur in relation to tapentadol and hydrocodone, which will present an improvement in the quality of life and cognition of patients.

Keywords: opioids; narcotics; cognition; cognitive dysfunction; chronic disease; abuse; substances

RESUMEN

Introducción: el impacto del uso crónico de opioides se ha relacionado con una amplia gama de desórdenes cognitivos, que abarcan desde deficiencias menores en habilidades cognitivas hasta problemas en habilidades como atención, aprendizaje, memoria y funciones ejecutivas.

Objetivo: realizar una revisión sistemática para investigar el impacto cognitivo en pacientes que usan opioides crónicamente y evaluar la gravedad de ese impacto. **Método:** se evaluaron ensayos clínicos aleatorizados, estudios de casos y controles, cohortes prospectivas y retrospectivas en dos bases de datos: PubMed y Cochrane Central, con la utilización de los siguientes términos en su búsqueda: "analgesic opioids", "cognitive dysfunction", "cognition impairments", "chronic disease" y "abuse, substance". La búsqueda fue en los idiomas inglés, español y portugués de estudios realizados en humanos adultos en uso crónico de opioides y su impacto cognitivo. **Resultados:** fueron seleccionados 7 estudios, 5 de los cuales los pacientes hicieron uso de tramadol y fue constatado el impacto cognitivo negativo, un estudio con el uso de tapentadol con impacto positivo sobre la cognición y un estudio con el uso de hidrocodona con impacto positivo en la neurocognición de los pacientes. **Conclusiones:** a pesar de las limitaciones encontradas, como conclusión se considera que el tramadol tiene un impacto negativo en la neurocognición, lo que no ocurre en relación con el tapentadol y la hidrocodona, que presentarán una mejoría en la calidad de vida y cognición de los pacientes.

Palabras claves: opioides; narcóticos; cognición; disfunción cognitiva; enfermedad crónica; abuso; sustancias

RESUMO

Introdução: o impacto do uso crônico de opioides tem sido relacionado a uma ampla gama de distúrbios cognitivos, desde pequenas deficiências nas habilidades cognitivas até problemas em habilidades como atenção, aprendizado, memória e funções executivas.

Objetivo: realizar uma revisão sistemática para investigar o impacto cognitivo em pacientes que fazem uso crônico de opioides e avaliar a gravidade desse impacto. **Método:** ensaios clínicos randomizados, estudos de caso-controle, coortes prospectivas e retrospectivas foram avaliados em duas bases de dados: PubMed e Cochrane Central, usando os seguintes termos em sua busca: "analgesicopioids", "cognitivedysfunção", "cognitiveimpairments", "doença crônica" e "abuso, substância". A busca foi em inglês, espanhol e português para estudos conduzidos em humanos adultos sobre o uso crônico de opioides e seu impacto cognitivo. **Resultados:** foram selecionados 7 estudos, 5 dos quais os pacientes usaram tramadol e foi verificado o impacto cognitivo negativo, um estudo com o uso de tapentadol com impacto positivo na cognição e um estudo com o uso de hidrocodona com impacto positivo na neurocognição de pacientes. **Conclusões:** apesar das limitações encontradas, como conclusão considera-se que o tramadol tem impacto negativo na neurocognição, o que não ocorre em relação ao tapentadol e hidrocodona, que apresentarão melhora na qualidade de vida e cognição dos pacientes.

Palavras-chave: opioides; narcóticos; conhecimento; disfunção cognitiva; doença crônica; Abuso; substâncias

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INTRODUCTION

The term opioid is used to denote a group of drugs with opium-like properties. Natural derivatives and some semi-synthetic congeners of opium alkaloids, which act on opioid receptors, are called opioids. There are several opioid agonists such as heroin, morphine and fentanyl, which are considered to be highly addictive.⁽¹⁾

Mu, Delta and Kappa (μ , δ and κ) opioid receptors are widely distributed throughout the nervous system. Opioids cause complex changes at the cellular and molecular level, decrease pain perception and increase tolerance to painful stimuli; other actions of opioids include euphoria, sedation, endocrine dysregulation and somnolence.^(2,3) Opioids also alter sleep regulation and are associated with poor sleep quality, observed alterations include: insomnia, respiratory depression, sleep apnea and respiratory disorders. Physiological dependence on opioids can develop rapidly after the use of these compounds. Increasing opioid dosage over time is a common and significant concern with this group of medications.^(4,5)

A growing body of evidence suggests that chronic substance users have higher rates of cognitive impairment than the general population. Numerous investigations have aimed to investigate the neurocognitive performance of people with various opioid-derived substance use disorders.⁽⁶⁾

Opioids are believed to worsen psychomotor task performance due to their sedative and mental "dulling" effects; as a result, some safety regulations currently restrict the use of opioids when driving or using heavy equipment.⁽⁷⁾

Long-term use of opioids raises concerns about possible adverse cognitive and psychomotor effects. The potential for such effects on cognitive function is suggested by the presence of opioid receptors in many areas of the brain that are involved in attention, memory, learning, and in everyday tasks, such as routine work tasks and safe driving of an automobile.⁽⁸⁾

Dramatic increases in the number of opioid prescriptions have been observed worldwide since the 2000's; in addition, there is the potential for serious adverse events as defined by the U.S. Food and Drug Administration (FDA): those with life-threatening outcomes, hospitalization, disability or permanent impairment, drug dependence or abuse, death or other life-threatening event, or requiring treatment to prevent such outcomes.^(9,10)

Opioids modulate the behavior of microglia, immune cells in the brain that mediate inflammation, which may contribute to neurodegenerative diseases; they also promote apoptosis of microglia and neurons. All of this evidence suggests that prolonged opioid use contributes to cognitive impairment.⁽¹¹⁾

Opioid use disorder is associated with cognitive dysfunction, and understanding how pharmacotherapy may affect cognition is an important consideration. Numerous investigations have aimed to investigate the neurocognitive performance of individuals with various substance use disorders, and evidence suggests that substance-using populations differ with respect to specific cognitive impairments.^(6,12) In this context, the present systematic review will seek to clarify the effects of chronic opioid use on neurocognition.



METHOD

A systematic review was carried out based on a research in PubMed and Cochrane Central digital platforms, in English, Spanish and Portuguese. The following terms were used: "analgesic, opioids", "cognitive dysfunction", "cognition impairments", "chronic disease" and "abuse, substance" in two different databases: PubMed and. A total of 220 articles were found: 159 belonging to PubMed and 61 to Cochrane Central.

The inclusion criteria were: randomized controlled trials, clinical studies and cohorts in English, Spanish and Portuguese; studies presenting chronic use of opioids and data on neurocognitive impact in humans were selected.

The exclusion criteria were: acute opioid use, studies that used another substance (cannabis, alcohol) other than opioids, studies in which the patients already had some dementia prior to opioid use (Alzheimer's disease, Parkinson's disease or HIV); studies in which the patients had some mental illness were also excluded, 170 articles were excluded and 16 were found.

The selected studies should report the elements of chronic opioid use and the cognitive impact of chronic opioid use. A total of 127 articles did not meet these criteria, so 7 were finally selected for analysis.

Of these, the following were analyzed: number of patients in the study, type of opioid used, dose, use, presence of neurocognitive impact, type of impact and adverse effects.

RESULTS

The present systematic review finally analyzed 7 studies on chronic opioid use and cognitive impact. In some studies, the only opioid used was tramadol^(5,13), which was the most studied opioid; other studies show an association of opioids such as morphine, methadone, ketobemidone, buprenorphine and tramadol.⁽¹⁴⁾

In the study by Sjogren, *et al.*⁽¹⁴⁾ 40 patients were studied, with an average age of 60 years, who received opioid doses averaging 60mg and were compared in their neuropsychological performance with 40 healthy people who did not use opioids by VAS scales (Visual Analogue Scales, by CRT (Continuous Reaction Time), PASAT (Paced Auditory Serial Audition Task) and the FTT (Finger Tapping Test).

The functions tested in these scales are considered high order cognitive functions. Patients with opioid use showed lower values in the CRT, i.e., worsening in that test; in the FTT they also obtained negative results, and with the PASAT scale they also had dizziness, hallucinations, sedation, pruritus, and constipation as adverse effects (Table 1).



Table 1. Cognitive impact studies on chronic opioid use

Study/Year	No. of patients	Opioid	Dose	Use	Neurocognitive Impact	Type of neurocognitive Impact/Adverse Effect
Sjogren, <i>et al.</i> 2000 ⁽¹⁴⁾	40	Morphine, methadone, ketobemidone, buprenorphine, tramadol, etc.	15-300 mg	Chronic	Yes	Dizziness, hallucinations, sedation, drowsiness
Mullican, <i>et al.</i> 2001 ⁽¹⁵⁾	462	Tramadol/paracetamol Codeine/paracetamol	37,5/325 mg	Chronic	Yes	Drowsiness
Babul, <i>et al.</i> 2004 ⁽¹³⁾	124	Tramadol	100-400 mg	Chronic	Yes	Drowsiness, dizziness, headache
Lee, <i>et al.</i> 2013 ⁽¹⁶⁾	245	Tramadol/paracetamol	75/650 mg	Chronic	Yes	Dizziness, headache, drowsiness
Bassiony, <i>et al.</i> 2017 ⁽⁵⁾	100	Tramadol	1125 mg	Chronic	Yes	Memory, visual skills, spatial skills, verbal fluency
Hale, <i>et al.</i> 2017 ⁽¹⁷⁾	330	Hydrocodone ER	30-180 mg	Chronic	No	-
Tarsitano, <i>et al.</i> 2019 ⁽¹⁸⁾	80	Tapentadol PR	25-500 mg	Chronic	No	-

In the study by Mullican, *et al.*⁽¹⁵⁾ 462 patients using tramadol/paracetamol and codeine/paracetamol were studied. The main adverse effect observed was somnolence; as well as Lee, *et al.*⁽¹⁶⁾ who used tramadol/paracetamol and studied 245 patients with adverse effects also with somnolence, but with the additional presence of dizziness and headache.

On the other hand, Bassiony, *et al.*⁽⁵⁾ in a study with 100 patients with tramadol use in which the cognitive impact was supported by the Montreal cognitive assessment test (MoCA), found that all patients with chronic use of tramadol showed an abusive use (1125 mg/day) had a significant worsening in all cognitive domains, the most affected were memory, visual and spatial skills and verbal fluency; patients who used tramadol had three times more neurocognitive dysfunction than controlled cases.

In the study by Hale, *et al.*⁽¹⁷⁾ 330 patients were studied with hydrocodone ER who were tested with the CAPF (Clinician Assessment of Patient Function), the PAF (Patient Assessment of Function), the BPI-SF (Brief Pain Inventory Short Form), the SDS (Sheehan Disability Scale), and the HPQ-SF (World Health Organization and Work Performance Questionnaire Short Form). In that study, patients had an improvement in all areas, such as general activities, walking and work, relationship, and exercise skills. There were no differences in the CAPF and PAF measurements.

The SDS indicated an improvement in functional status on hydrocodone treatment. The overall study showed an improvement of patients treated with hydrocodone in functioning, disability, life and productivity; also an improvement in productivity at work, affective and sexual life.



The work of Tarsitano, *et al.*⁽¹⁸⁾ evaluated tapentadol PR as an opioid in 80 patients and used the MMSE (Mini-Mental State Examination) to evaluate cognitive disability. The test on this scale showed more stable values in the patients who used tapentadol, without significant variability, with improvement in anxiety and depression; both in the physical and mental evaluation they had improvement with the medication. The data available from this review do not allow a meta-analysis to be performed.

DISCUSSION

Opioids are often considered the major culprits of cognitive impacts in patients both in regulated use and abuse, hence the need to study the subject and analyze their impact.

Studies with tramadol^(5,13-16) indicate the cognitive impact in patients who make chronic use of this medication, mainly and with more impact Bassiony, *et al.*⁽¹⁵⁾ who used the MoCA test for this purpose, which objectively shows what type of neurocognitive impact their patients presented. It should also be noted that in Bassiony's work, the daily tramadol dose was 1125 mg, an abusive use of the medication and in which the negative results were much more intense than in the other studies, such as that of Sjogren, *et al.*⁽¹⁴⁾ where the maximum dose was 300 mg.

In comparison, the study by Lee, *et al.*⁽¹⁶⁾ in which the approach was somewhat more subjective and tramadol was associated with paracetamol at a dose of 75/650 mg.

The limitations of this work were also noted in the aspect of comparison between types of cognition tests with the respective use of MoCA, others with use of the MMSE⁽¹⁸⁾ or the SDS.⁽¹⁷⁾

In the tapentadol study, the age range of the patients, who were on average 80 years old, should be highlighted as a limitation.

CONCLUSIONS

Despite the limitations found, it is considered that tramadol has a negative impact on neurocognition, which does not occur in relation to tapentadol and hydrocodone, which showed an improvement in the quality of life and cognition of the patients.

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The authors declare that there are no conflicts of interest.

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