Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 140

The gut-brain axis in medication overuse headache: an integrative review

Leandro Miranda Campos, Érica Brianne Tavares de Lima, Sanjhones Gabriel Souza Leite, Daniel Lemos Neto Rodrigues, Paula Alves Bezerra Carolyne, Wagner Horta Gonçalves

Olinda School of Medicine, Olinda, Pernambuco, Brazil

Daniel Lemos Neto Rodrigues
danieldede3@hotmail.com

Introduction
Medication Overuse Headache (MOH) represents a significant clinical challenge, characterized by the chronification of pain in individuals who excessively use analgesics. Although the pathophysiology of MOH has traditionally focused on pharmacological aspects, the current understanding of pain neurobiology has expanded to include the complex interaction between multiple systems. In this context, the potential influence of the gut-brain axis on the perpetuation of pain in MOH has emerged as an area of growing interest, requiring a synthesis of evidence that may guide future investigations and therapeutic approaches.

Objective
To analyze the scientific evidence regarding the involvement of the gut-brain axis in the pathophysiology of MOH.

Methods
An integrative literature review was conducted using PubMed and BVS databases (English and Portuguese language publications) between 2021 and 2025, following PRISMA guidelines. DeCS/MeSH descriptors included: "Medication Overuse Headache," "Rebound Headache" and "Drug-Induced Headache," combined with "microbiota," "gut-brain axis," and "leaky gut". Inclusion criteria comprised clinical trials, observational studies, and experimental studies involving humans and animal models. Exclusion criteria included duplicate studies, non-original studies, and studies not directly related to the topic. The final sample consisted of 9 articles.

Results
The analyzed studies demonstrated convergence in indicating that MOH is a condition mediated by the gut-brain axis. Chronic analgesic use, especially nonsteroidal anti-inflammatory drugs (NSAIDs), was associated with intestinal mucosal injury and increased intestinal permeability ("leaky gut"), favoring the translocation of lipopolysaccharides (LPS) into the systemic circulation. The resulting low-grade endotoxemia induced a persistent inflammatory response, with increased levels of IL-6, IL-17, HMGB1, and CGRP, all associated with neuroinflammation, trigeminal sensitization, and trigeminovascular hyperexcitability. These alterations were associated with reduced pain threshold, increased headache frequency, and headache chronification. In addition, psychiatric comorbidities and dietary factors were associated with dysregulation of the gut-brain axis in MOH.

Conclusion
The evidence indicates that the gut-brain axis contributes to the pathophysiology of MOH. Chronic analgesic use, associated with disruption of the intestinal barrier and low-grade endotoxemia, constitutes a mechanism related to neuroinflammation, trigeminal hyperexcitability, and pain chronification. These findings reinforce the importance of further research and suggest intestinal microbiota modulation as a potential therapeutic target in MOH.

Keywords:
Pathophysiology
Gut-brain axis
Medication overuse headache

© Copyright 2025