



# Codeine, Heightened Pain Sensitivity and Medication Overuse Headache:

A Neuroimmune Hypothesis and Novel Treatment Strategy

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## **ABSTRACT**

Codeine is the most widely consumed opioid analgesic worldwide. It relies upon partial metabolism to morphine to elicit analgesic effects. Paradoxically, the pain-reliever morphine has previously been linked to states of increased pain sensitivity; such as medication overuse headache and opioid-induced hyperalgesia and allodynia.

Despite the clinical impact of medication overuse headache the pathophysiology behind this disorder remains unclear and mechanism-based treatments are lacking. Although most acute headache treatments are alleged to cause medication overuse headache, within this thesis we conclude from the literature opioids are the drug class most strongly associated with worsening headache. In opioid-induced hyperalgesia and allodynia sensitivity to normally noxious, and non-noxious stimuli respectively, are enhanced due to opioid exposure.

Chronic morphine may exacerbate pain in the long-term by non-specifically activating toll-like receptor-4 (TLR4) on glial cells, resulting in a pro-inflammatory state that manifests clinically as increased pain. Here we hypothesise medication overuse headache is a specific form of opioid-induced hyperalgesia, which derives from a cumulative interaction between central sensitisation and glial priming, due to repeated activation of nociceptive pathways by recurrent headaches, and pain facilitation due to glial activation and subsequent neuroinflammation.

The first part of this thesis examines the efficacy of a glial-attenuating treatment, ibudilast, in the clinical management of medication overuse headache induced by opioid use in a double-blind, randomised, placebo-controlled parallel group study. Patients received ibudilast 40 mg twice daily or placebo for 8 weeks and recorded headache and analgesic intake using a headache diary for 4-weeks prior to randomisation and throughout the treatment phase.

No reduction in headache burden, opioid analgesic intake or headache related quality of life were observed in the ibudilast group compared to placebo, however, valuable safety data were obtained

demonstrating ibudilast 80 mg/day is well tolerated, facilitating the use of similarly high doses in future studies for alternative indications.

Prior to this PhD project the relationship between codeine and increased pain sensitivity had not been investigated. *In silico* docking simulations performed as part of this PhD suggest codeine binds to MD2, an accessory protein for TLR4, signifying it may be able to induce hyperalgesia independent of conversion to morphine. Evidence that codeine can induce hyperalgesia would sit in line with our glial hypothesis for opioid overuse headache. Thus, the second part of this PhD includes a series of preclinical experiments to 1) determine if chronic codeine alters pain sensitivity 2) ascertain if pre-existing glial activation primes for opioid-induced hyperalgesia, 3) investigate signalling pathways involved and 4) assess potential interventions to reverse exacerbated pain sensitivity. Hyperalgesia and allodynia were measured using hot plate and von Frey tests respectively, at baseline, day 3 and day 5 in mice receiving intraperitoneal codeine 21 mg/kg, morphine 20 mg/kg or saline, twice daily.

Our preclinical studies demonstrate that despite providing lesser acute analgesia, equimolar codeine and morphine induced similar hot plate hyperalgesia, suggesting codeine does not rely upon conversion to morphine to increase pain sensitivity, emphasising the non-opioid receptor-dependent nature of this phenomenon. IL-1RA reversed codeine-induced hyperalgesia and allodynia, and knock-out of TLR4 protected against codeine-induced pain sensitivity changes. Glial attenuation with ibudilast reversed codeine-induced allodynia and thus could be investigated as potential treatment for conditions involving codeine-induced pain enhancement.

## DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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## LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
5-HT	5-Hydroxytryptamine, serotonin
CCI	Chronic Constriction Injury
CD11b	Cluster of Differentiation Molecule 11B
CYP	Cytochrome P450
DAMGO	D-Ala <sup>2</sup> ,N-Me-Phe <sup>4</sup> ,Gly- <sup>o</sup> 5 enkephalin
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Edition IV
GFAP	Glial Fibrillary Acidic Protein
HAD	Hospital Anxiety and Depression
ICHD-I	International Classification of Headache Disorders, First Edition
ICHD-II	International Classification of Headache Disorders, Second Edition
ICV	Intracerebroventricular
ID	Intradermal
IL	Interleukin
IT	Intrathecal
IV	Intravenous
MDQ-H	Medication Dependence Questionnaire in Headache patients
MIDAS	Migraine Disability Assessment
MOH	Medication Overuse Headache
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PBMC	Peripheral Blood Mononuclear Cell
PREEMPT	Phase III REsearch Evaluating Migraine Prophylaxis Therapy
SC	Subcutaneous
SD	Sprague-Dawley
SF-36	Short Form 36 (36 items)
TLR	Toll-Like Receptor
TLR2	Toll-Like Receptor 2
TLR4	Toll-Like Receptor 4
TNF- $\alpha$	Tumor Necrosis Factor $\alpha$
TTH	Tension Type Headache
US	United States

## LIST OF PUBLICATIONS DURING CANDIDATURE

**Johnson, J**, Rolan, P, Johnson, M, Bobrovskaya, L, Johnson, K, Tuke, J, Williams, D &

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