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Opioid connections: to analgesia, addiction and beyond

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Main Points

Pain physiology

The endogenous opioids system (EOS)

Opioid Use Disorder (OUD): nosology and approach

Pain management

The meaning of life



Pain Physiology

Rene Descartes' 1662 theory of pain



While damage provides nociceptive input, we now know pain is far more complex.



As pain becomes chronic, functional-MRIs shows it ceases to involve the sensory areas responding to acute peripheral pain. Other areas dampen or amplify the chronic pain experience:

- Endogenous Opioid System (EOS),
- Limbic system (emotions, motivations, learning & memory)



The importance of cognitive science in pain

Brain activity following nociception indicates cortical executive function selects:

- which stimulus receives attention
- how evaluation is based on context, experience circumstance, expectation and need
- which motor response is best

Legrain Clin Neurophys 2012;

“In other words, pain is a learned phenomenon.”

Ballantyne BMJ 2025

“Pain should be now seen more as a response to threat than to damage”. Sullivan Pain 2022



Thomas Hobbes (1588-1679) argued life without society would be “solitary, poor, nasty, brutish, and short”

Brain and opioid science

Our EOS has many functions including the modulation of physical and psychosocial pain. It may provide relief or reward: the same as exogenous opioids.



Some theorists argue, the primary role of pain is to modulate anti-social behaviour Vs social behaviour (eg group formation) via social reward and social pain.

Carr Pain Medicine 2017

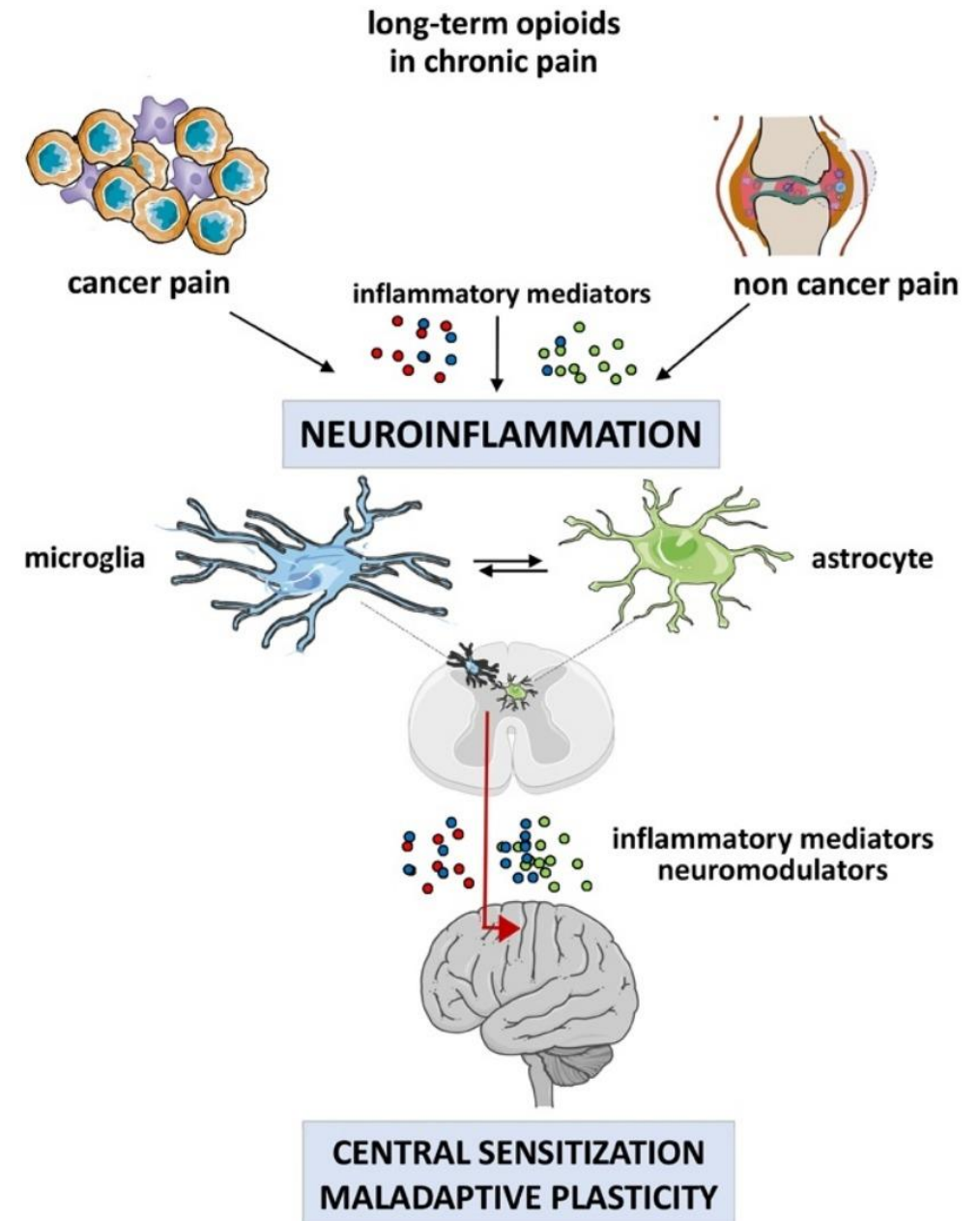
This would offer evolutionary advantage for the survival of both individual and tribe. Showing altruism to kin may benefit an individual when they themselves are suffering. Sullivan Pain 2025

When we swamp the EOS with exogenous opioids, we change the modulation of physical and social pain and reward.

It should be no surprise then that providing opioid analgesics may trigger more socially destructive behaviours as described by the criteria for OUD.

The EOS, the immune system and cancer

- Opioids are considered stress hormones of the cytokine family - inflammatory mediators.
- Exogenous opioids seem to hijack this neuroimmune network. Resultant neuroinflammation risks making chronic non-cancer pain become malignancy-like pain Santoni Cancers 2022
- In cancer cells, the tumour microenvironment has many opioid receptors. Exogenous opioids trigger neuroinflammation and potentially tumour growth, worsening pain and metastases Santoni Cancers 2022



Naloxone studies identify many EOS functions including:

"Runners' High" or exercise-related hypoalgesia

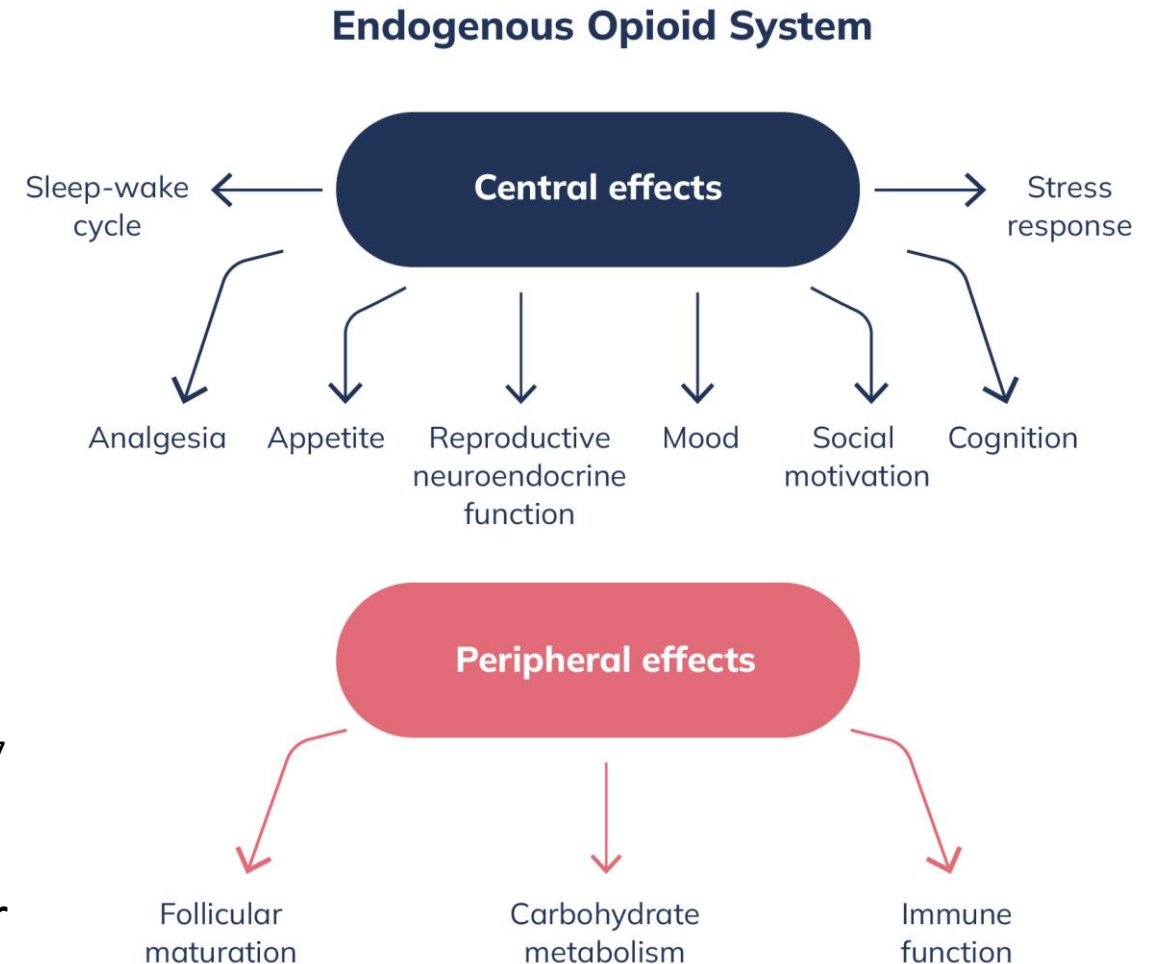
Bruehl Pain 2020

Brief analgesia from vaping Bremmer 2025 Psychopharmacology

Placebo analgesia Livrizzi bioRxiv 2025

EOS deficiency can be associated with:

- Eating disorders including both anorexia nervosa and binge eating Sutton Hickey Nature Comms 2025
- A tendency to verbal & physical anger Burns J Pain 2017
- Higher depressive/anxiety symptoms, pain catastrophizing, perceived disability and a greater opioid analgesic response. Burns PAIN 2017
- Non-suicidal self-injury Johnson Curr Pain Headache Rep 2022



Opioid analgesics cause harms beside OUD including the worsening of pain as shown by:

- A randomized 12-month trial which found opioid care gave worse outcomes than nonopioid care
Krebs J Gen Int Med 2017
- A consensus systematic review from the US National Institutes of Health Chou Annals of Internal Medicine 2015
- Demographic data: the prevalence of “**any** pain” increased from 49% to 54% between 2002-2018 in USA adults Zajacova Demography 2021
- Population studies: Those with chronic pain on prescription opioids had worse pain and function & higher healthcare USE Eriksen Pain 2006
- Animal-model studies show opioids increase the rate that acute pain becomes chronic
Green-Fulgham PAIN 2019



Opioid Use Disorder: nosology

OD criteria were created from studies of heroin users at addiction clinics. They are less helpful for prescription opioid use disorder.

Experts argue we should remove tolerance and withdrawal if patients are taking the analgesics as directed.

Experts debate if we should exclude any DSM-V criteria based on patient motivation.

Should we ignore behaviours motivated to relieve pain but include behaviours where the motivation is to get high or to cope with anxiety or depression. Hasin Am J Psychiatry 2022

DSM V criteria

- Tolerance
- Withdrawal symptoms
- Using more than intended
- Wanting to cut down or stop without success
- Opioids dominating time
- Craving
- Neglecting responsibilities
- Social or interpersonal problems
- Withdrawing from activities
- Using in risky situations
- Continuing use despite known problems

Opioid Use Disorder

Is trying to diagnose prescription OUD a waste of time? Jones
Cancer 2022

If we do diagnose OUD, what should we do?

- Stop providing opioids? (leaving patients abandoned)
- Refer them to an addiction clinic?

Rather than focus on heroin-like harms, we need to consider that overdoses and other harms occur across the spectrum of OUD criteria and are strongly associated with dose and duration. Sullivan & Ballantyne Am J Psychiatry 2022

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Let's move towards a more integrated approach between pain care and addiction care



- Stop initiating opioids for chronic pain
- Ensure any opioid provision has routine safety boundaries (i.e. methadone-program-like strategies)
- Exclude suicidality and self-harm
- Reduce polypharmacy (especially benzodiazepines)
- Avoid rapid weaning of opioids. Maximum rate should be 15% per 2 months Metz J Gen Int Med 2024
- Prioritise non-pharmacological therapies (or at least non-addictive medications) and use multi-modal management for patients' multi-morbidities.

Pain management

Firstly, reassurance and empathy.

Agree that they do feel better after their opioids and they do feel desperate pain without them.

Plan the introduction of multi-modal, multi-disciplinary, holistic care to support the multi-faceted EOS.

Social Prescribing, for example, may include recommending Parkrun. This free weekly run or walk facilitates movement, fitness, fun and socialisation.

Prescribing wellness: comprehensive pain management outside specialist services

SUMMARY

Opioids have important roles in the time-limited treatment of acute and cancer pain, end-of-life pain or dyspnoea, and in opioid dependency.

Maintaining focus on biomedical treatments, including drugs, has limited success in chronic pain.

Active self-management and healthy lifestyle choices are fundamental to addressing multisystem complexity and harnessing neuroplasticity in chronic pain.

Addressing psychosocial maladaptations and physical deconditioning requires a variety of approaches, frequently involving multiple care providers.

In practice, most pain care is delivered outside specialist centres by GPs and other non-pain specialists. Although they are well placed to provide multimodal care, they often lack training and confidence in delivering this care.

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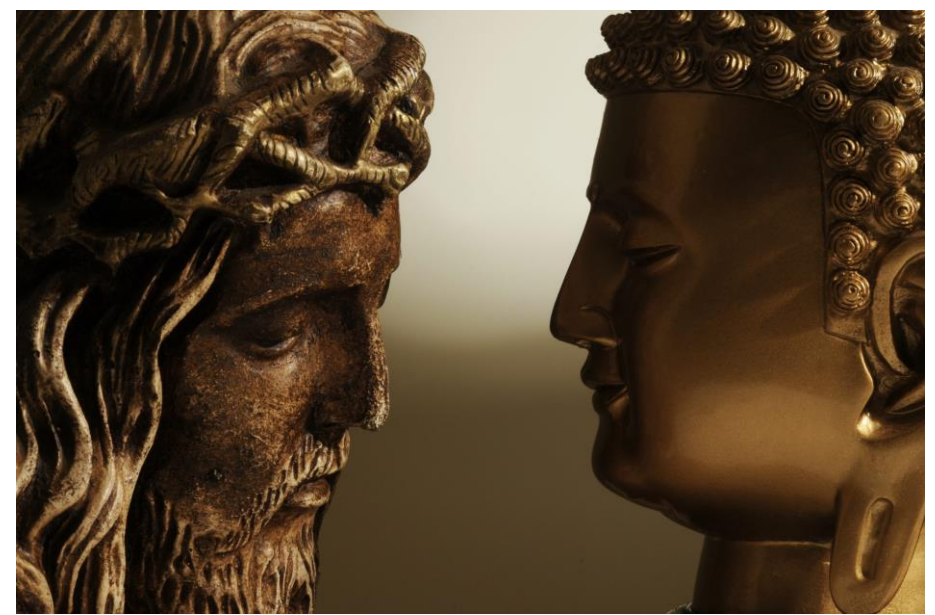
Holliday 2018
Australian
Prescriber



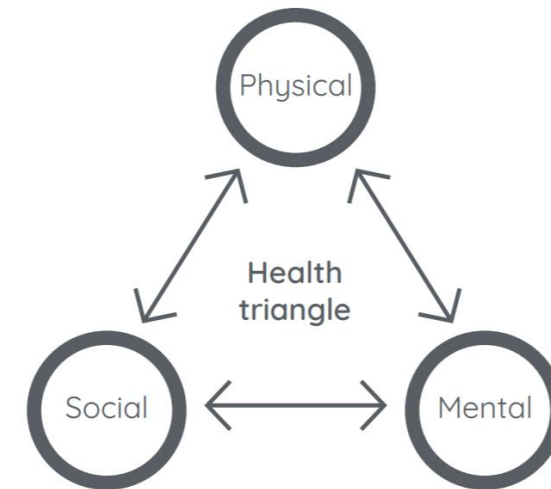
And now for the Meaning of Life

George Vaillant followed up 268 Harvard University students over 75 years. This was a landmark study particularly about alcoholism.

In a subsequent 2012 unpublished manuscript, he reflected that the work revealed that the key ingredients that lead to a rewarding life (as defined by good physical, mental and social health aged 50-80) was the capacity for loving attachment.



**75 Year-Long Harvard
Study Reveals The
Secret to
Happiness**



Conclusion

Pain functions as a response to a threat to individual and kin.

Our EOS modulates physical and social pain & reward: as do exogenous opioids.

Opioid analgesics swamp/hijack these EOS functions, skewing psychosocial function to resemble the criteria for OUD.

Attempting an OUD diagnosis requires disentangling pain relief from psychosocial relief. This can be a distraction.

Good pain care focuses on restoring function and quality of life rather than reducing pain intensity.

Integrating this with good opioid care involves harm minimisation, and potentially a slow wean.

