The science of pain and addiction

Why opioids don’t work well for chronic pain

JANE C BALLANTYNE

UNIVERSITY OF WASHINGTON, SEATTLE
Failure to appreciate the necessary partnership between pain and reward (pleasure) means:

1. Pain is misunderstood

2. Addiction is misunderstood

3. Pain and addiction interactions are misunderstood
• Plato and Aristotle considered pain not a sensory experience, but associated with emotions and appetites

• Pain was the opposite of pleasure

• Pain was something external that descended upon the person

• This idea of pain as a spiritual punishment persisted for millennia

• Although detailed anatomy of the nervous system has been worked out, its function had not
Descartes changed everything

- Early reductionist view
- First to describe pain as a perception, existing in the brain
- Dualist believing in the separation of mind and body
- The ringing of a bell, distinguished from sensory transduction

L’homme de Rene Descartes. Paris: 1664
Towards a reductionist view of pain

1837 Purkinje
Microscopy opened up a whole new understanding

1906 Sherrington
Neuron theory, electrical conduction of neural signals

1990s
Led to identification of specific pathways

Towards a reductionist view of pain
Towards a reductionist view of pain

Until Descartes, external events caused pain

Anatomy of pain not understood
Microscopic events not understood
Existence of endogenous opioids not even imagined

Digging deeper and deeper into the minutiae

Reductionist viewpoint

Impersonal, mechanistic terms
Focus on nociception

*Mechanism based treatment*
“Many investigators seem grimly determined to establish ....that for a given stimulus there must be a given response; that is, for so much stimulation of nerve endings, so much pain will be experienced, and so on.

This fundamental error had led to enormous waste. It is evident ..... that there is no simple relationship between stimulus and subjective response.

It is also made evident that the reason for this is the interposition of conditioning, of the processing component, of the psychic reaction.”

Beecher HK  Increased stress and effectiveness of placebos and “activity” drugs  Science 132;91-2 July 1960
• Gate control theory of pain
• Pain not transmitted along a line-labelled system
• Pain neuroplastic

Melzack and Wall  Science 1965;150:971-9
Endogenous opioid system through the lens of addiction

Pathological
OPIUM

narcotic actions

morphine  papaverine  codeine  narcotine  thebaine

50%

strychnine-like actions
1960s-1970s

- Researchers in Addiction Research Center proposed opioid receptors purely on the basis of pharmacological studies

Early 1970s

- Researchers identified specific opioid receptors in brain and peripheral tissues

Mid-1970s

- The fact that the receptors were highly sensitive to morphine led to search for and discover of endogenous opioids

Martin WR et al  J Pharmacol Exp Ther 1976;197:517-32
Lord JAH et al  Nature 1977;267:495-9

Pert CB and Snyder SH  Science 1973;179:1011-14
Pert CB and Snyder SH  Mol Pharmacol 1974;10:868-79
Simone EH et al  Proc Natl Acad Sci 1973;70:194709

Hughes I et al  Nature 1975;258:577-79
Goldstein A et al  Proc Natl Acad Sci 1979;76:666-70
Bradbury A et al  In: Proc Fourth Am Peptide Symposium
What is addiction and how is it diagnosed?

Addiction is an irreversible neurobiological disease characterized by craving

To fulfill today’s DSM or ICD criteria you need:

• Tolerance
• Withdrawal (physical dependence)
• At least one aberrant behavior categorized as social disruption, loss of control over use, continuous use despite harm and craving
Before 1950s
- Addiction considered weakness of character, not a medical illness

1950s
- First DSM substance abuse grouped under Sociopathic Personality Disturbances
- Key role of tolerance and dependence not recognized

1970s
- Discovery of endogenous opioid system
- Recognition that endogenous opioids are central to reward and addictions

1980s
- Key role of tolerance and dependence recognized
- DSM-III tolerance and dependence included
The endogenous opioid system through the lens of pain and survival

Natural and integral
At rest

Injured
(analgesic but tender)

In chase

In chase
Pain and opioid pathways and actions

Opioid induced hyperalgesia

Ballantyne & Mao NEJM 2003;349:1943-53
Mao Pain 2002;100:213-7
Central control (top down) contributes as much as nociception to the experience of pain and is a powerful means of controlling pain.

Opioid systems are intimately involved in the top down effects and in socialization.

Disruption of social attachments, particularly maternal-infant attachments is one of the primary causes of “social and emotional pain”.

Isolation, withdrawal, distress, family, job, culture all influence the development of chronic pain and are indicators of derangement in natural (opioid) systems.
Current theories about the purposes of the endogenous opioid system:

- The system provides stress-related pain relief and pain enhancement (injury-related “physical pain”)

- It also facilitates maternal-infant and other attachments

- The pain and opioid systems are one and the same and evolved through evolutionary processes over millions of years
Until Descartes, external events caused pain

Anatomy of pain not understood
Microscopic events not understood
Relationship to endogenous opioid system not understood

Digging deeper and deeper into minutiae

Reductionist viewpoint

Impersonal, mechanistic terms
Focus on nociception
**Mechanism based treatment**

Encompassing yet transcending minutiae

Importance of the dysphoric social dimension

Isolation, withdrawal, distress
Group processes - family, job, culture

**Public health, strengthening communities, teams, systems**
When in the 1980s-90s we started promoting chronic opioid therapy, we thought it would not be addictive

• Addiction is rare when treating pain with opioids

• Dependence is “physical” and easily reversed

Porter and Jick NEJM 1980;302:123
Portenoy and Foley Pain 1986;25:171-86
Dependence on opioid analgesics ≠ Addiction, substance dependence or substance use disorder
YET:
If opioids are used long-term and continuously, neuroadaptation with many similarities to addiction is inevitable

- Physical – regions of control of somatic function - locus ceruleus (noradrenergic nucleus)
  
  upregulation of cAMP $\leftrightarrow$ arousal, agitation, diarrhea, rhinorrhea, piloerection

- Emotional/psychological – reward centers
  
  hedonia $\leftrightarrow$ anhedonia

- Pain pathways
  
  analgesia $\leftrightarrow$ hyperalgesia

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Ballantyne & LaForge, Pain 2007;129:235
Ballantyne et al, Arch Int Med 2012;172:1342
• Tolerance and dependence are combined neuroadaptations
• Tolerance and dependence explain analgesic failure
• Analgesic failure = no dose is enough
Enduring adaptations produced by continued drug use together with established behaviors

For the illicit drug user:

- Procurement behaviors

For the pain patient – much more complex:

- Continuous opioid therapy may prevent opioid seeking
- Memory of pain, pain relief and possibly also euphoria
- Even if the opioid seeking appears as seeking pain relief, it becomes an adaptation that is difficult to reverse
- It is hard to distinguish between drug seeking and relief seeking

Nestler Neuron 1996;16:897
Nestler Neuropharmac 2004;47 Suppl 1:24
Cami & Farre NEJM 2003;349:975
**Dependence/addiction develops through pain treatment**

- *Pester ing reluctant doctors*
- Using opioid to treat pain
- Predominant symptom of withdrawal - *pain*

**Dependence/addiction develops through recreational drug use**

- *Need to procure opioid*
- Often use paraphernalia
- Predominant symptom of withdrawal - *anhedonia*

**DSM Criteria**

- Social disruption
- Loss of control over use
- Continued use despite knowledge of harm
- (Craving) *(may not be manifest until off)*

Do not accept that anything is wrong other than pain

Accept that they are addicted

*Ballantyne & LaForge*  
*Pain* 2007;129:235-55
Dependence on opioid pain medications

- Nobody wants to call it addiction
- It doesn’t look like addiction

BUT

- It is pathological
- It does destroy lives
- It is avoidable, and it is treatable

No bright line between dependence and addiction

Dependence and addiction definitions:

**ADDICTED**
- Meets DSM criteria for addiction

**NOT ADDICTED**
- No lost prescriptions
- No ER visits
- No early prescriptions
- No requests for dose escalation
- No UDT aberrancies
- No doctor shopping (PMP)
The last decade’s advances in the science of pain and opioids show that the early Greek philosophers were deeply insightful: persistent pain has more to do with emotions and appetites than with sensation.
State-dependent opioid control of pain
(linkage of circumstance and behavior to pain)

Pain is primarily a motivational state that has a powerful influence on decision making

- Because the biologically relevant output of the nervous system is behavior, circuits are meaningfully defined in relation to a specific behavior
- Opioids can either relieve or worsen pain, depending on behavioral state, even when only one receptor (or circuit) is involved

‘on’ cells → burst of activity
(facilitate nociceptive transmission)

‘off’ cells → pause in firing
(inhibit nociceptive transmission)

Fields, Nature Rev Neurosci 2004;5:565
Pronociception = pain chronification and opioid hyperalgesia

Common mechanisms:

- Receptor trafficking
- Intracellular signaling
- NMDA neurotransmission
- Epigenetic changes
- Opioid induced neuroinflammation
- Latent pain sensitization

Ballantyne PAIN 2016 Aug 10, epub ahead of print
Rivat & Ballantyne Pain Reports 2016;1:e570
fMRI and biochemical measurement confirms the emotional component of pain

- Dysphoric social dimension
- Isolation, withdrawal, distress
- Contributing as much as nociception
Relief from pain in humans is rewarding and pleasurable.

• Primary rewards, or reward-predictive cues, are encoded in brain reward/motivational circuits.

• Relief of aversive states, including pain, often promotes a positive emotional state.

• Rewarding features of pain relief likely facilitate learning about actions leading to relief.

“Happiness is not being pained in body or troubled in mind.”
Thomas Jefferson
Pain is misunderstood

Nociception is not pain
Pain and opioid systems are integrated and inseparable
Pain is a motivational state that modulates behavior

Addiction is misunderstood

Drug addiction arises because of neuroadaptation (maladaptation)
Adaptation is to continued drug use coupled with drug seeking behaviors
A similar adaptation can occur with opioid pain treatment
There is no bright line between dependence and addiction

Pain and addiction interactions are misunderstood

Pain and pleasure (reward) exist in a balance
Pain and pleasure (reward) mediate adaptation and survival
Exogenous opioids overwhelm and disable natural opioid systems
What might have changed if we had understood better?

- We may have questioned the role of exogenous opioids if we had a mature understanding of the vital role of the endogenous opioid system in mediating pain, pleasure and social behavior.

- We may have been more selective in prescribing chronic opioids if we understood that the people at greatest risk of developing dependence on opioid analgesics are the very people whose chronic pain has its roots in social disruption (the opioid quandary).

- We may have been more circumspect if we had understood that although opioids may be the only thing that relieves pain for high risk individuals, the price is the disruption of the endogenous opioid system.

- We may have been more inclined to address the root causes of chronic pain, especially social disruption, had we understood the importance of their role in creating chronic pain.