Smoking and Chronic Pain: Physiological and Clinical Correlations

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Disclosures

• None
Objectives

• Discuss nicotinic and opioid receptor interactions
• Identify associations between smoking, opioid use and pain severity
• Discuss smoking cessation, chronic pain and treatment outcomes
After all these years, why are we still talking about smoking?
The Cigarette Death Epidemic in Perspective

- Annual smoking deaths
- Environmental tobacco deaths
- U.S. WWII deaths
- Annual auto accidents
- Vietnam War
- AIDS 1983-1990
- Annual murders
- Annual heroin/cocaine deaths
Do we really need to talk about receptors?
Smart Phone Neuron

apps

Apps receptor
Cigarette smoke (nicotine)

- Thalamus
- \( \alpha 4\beta 2^* \quad \alpha 7 \)
- Dopamine release in striatum/nucleus accumbens
- N.Epi release in hippocampus/thalamus

- \( \alpha 7 \quad \alpha 4\beta 2^* \)

- N. raphe magnus/Dorsal raphe/Locus ceruleus

- Opioid release
- Serotonin release

- Inhibit
- Modulate

- Ketamine
- Volatile anesthetics
- Phencyclidine
- Local anesthetics
- Neurosteroids

- \( \alpha 9\alpha 10 \quad \alpha 4\beta 2^* \)

- Opioid release
Antinociception and Nicotine in Animal Models

Fact Check

- Antinociception **blocked** by naltrexone
- Antinociception **reduced** in mu-opioid receptor knock-out mice
- Morphine induced antinociception **enhanced** by nicotine administration
- Chronic nicotine administration is associated with **up-regulation** of mu-opioid receptors
Scott DJ. Neuropsychopharmacology 2007;32:450-7
Does smoking cause chronic pain?

“...smoking...considered to be a weak risk indicator and not a risk factor for chronic low back pain.”
Smoking as a Risk Factor for Chronic Pain

OR = 3.4  Kaila-Kangas. Spine 2003;28:1860
OR = 2.6  Mikkonen. Spine 2008;33:527
OR = 2.3  Eriksen. Scand PHC 1999;17:174
OR = 1.6  Power. Am J PH 2001;91:1671
OR = 1.5  Manttila. Eur Spine J 2008;17:1317
OR = 1.4  Manttila. Pain 2008;139:209
Modifiable risk factors for incidence of pain in older adults

Yu Shi a, W. Michael Hooten a,b, Rosebud O. Roberts c, David O. Warner a,*

a Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA
b Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
c Division of Epidemiology, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN, USA
Depression
Overweight
Pain
Smoking → Pain
Depression

Smoking ≠ Pain

“…smoking increased the likelihood of incident pain only among subjects who reported depression.”
Do smokers have greater pain severity?
Smoking

Pain Severity
Comparison between Smokers and Nonsmokers

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Smoking Status</th>
<th>Male</th>
<th>Female</th>
<th>Painful Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverstein</td>
<td>1982</td>
<td>Deprived</td>
<td>38 + 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perkins</td>
<td>1994</td>
<td>Deprived</td>
<td>10 + 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 + 6</td>
<td>6 + 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 + 9</td>
<td>9 + 9</td>
<td></td>
</tr>
<tr>
<td>Jamner</td>
<td>1998</td>
<td>Deprived</td>
<td>17 + 13</td>
<td>21 + 23</td>
<td></td>
</tr>
<tr>
<td>Girdler</td>
<td>2005</td>
<td>Not deprived</td>
<td>20 + 20</td>
<td>17 + 20</td>
<td></td>
</tr>
</tbody>
</table>

Cold Pressor
Th –

Electrical
Th –
Th 0

Thermal Heat
Th 0

Th + T +

Ischemia
Th + T + (males only)

Th 0, T 0 (males only)

Th T + (females only)

“Deprived” smokers were abstinence from smoking for at least 3 h before the experiment. “Not Deprived” smokers maintained smoking throughout the experimental period.

+ = higher in smokers; – = lower in smokers; 0 = no difference between smokers and nonsmokers; T = tolerance; Th = threshold.

Shi Y. Anesthesiology 2010;113:977
Effects of Smoking Status on Pain Severity

Hooten WM. Anesthesia & Analgesia 2009;108:308
Effects of Smoking Status on Pain Severity

Hooten WM. Anesthesia & Analgesia 2009;108:308
What about the potential effects of depression?
Depression → Chronic Pain
Chronic Pain → Depression
Chronic Pain  ↔  Depression
A. Depression ↔ Chronic Pain

B. Depression → Pain Severity

C. Depression → Smoking
The effects of depression and smoking on pain severity and opioid use in patients with chronic pain

W. Michael Hooten a,b,*, Yu Shi c, Halena M. Gazelka d, David O. Warner a
Baseline scores of the Centers for Epidemiologic Studies-Depression scale (CES-D) and Multidimensional Pain Inventory (MPI) pain severity subscale based on smoking status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current smoker (n = 313)</th>
<th>Former smoker (n = 294)</th>
<th>Never smoker (n = 634)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D Baseline</td>
<td>30.2 ± 12.5\textsuperscript{a,**}</td>
<td>26.1 ± 11.9\textsuperscript{b}</td>
<td>25.0 ± 12.2\textsuperscript{b}</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MPI pain severity</td>
<td>49.8 ± 9.8\textsuperscript{a}</td>
<td>47.8 ± 9.0\textsuperscript{b}</td>
<td>46.9 ± 9.4\textsuperscript{b}</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Univariate analysis of variance.
** Mean ± SD; different superscripts denote Tukey honestly significant difference post hoc statistical significance (P < .05) between groups and similar superscripts denote no statistical significance.

Hooten WM. Pain 2011;152:223
Smoking → Pain Severity
“...baseline pain severity was independently associated with greater levels of depression, but not with smoking status.”
Linear regression analyses with baseline MPI pain severity as the outcome variable.

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>β Coefficient in univariate analysis (95% CI)</th>
<th>P value</th>
<th>β Coefficient in multivariate analysis* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>.00</td>
<td>.197</td>
<td>.00 (-1.29 to 1.17)</td>
<td>.922</td>
</tr>
<tr>
<td>Former</td>
<td>.86 (-.45 to 2.18)</td>
<td>.197</td>
<td>-.06 (.76 to 1.78)</td>
<td>.427</td>
</tr>
<tr>
<td>Current</td>
<td>2.89 (1.58 to 4.20)</td>
<td>&lt;.001</td>
<td>.51 (.21 to 2.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CES-D score</td>
<td>.28 (.23 to .31)</td>
<td>&lt;.001</td>
<td>.25 (.21 to .29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>.65 (-.81 to .97)</td>
<td>.196</td>
<td>.66 (.71 to .34)</td>
<td>.137</td>
</tr>
<tr>
<td>Female sex</td>
<td>-.45 (-1.70 to .79)</td>
<td>.474</td>
<td>-.41 (-1.56 to .74)</td>
<td>.485</td>
</tr>
<tr>
<td>Married</td>
<td>-.74 (-1.87 to .39)</td>
<td>.201</td>
<td>-.83 (-1.92 to .26)</td>
<td>.137</td>
</tr>
<tr>
<td>Years of education</td>
<td>-.69 (-.89 to -.50)</td>
<td>&lt;.001</td>
<td>-.53 (-.71 to .34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Currently employed</td>
<td>-4.45 (-5.62 to -3.29)</td>
<td>&lt;.001</td>
<td>-2.72 (-3.84 to -1.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain duration</td>
<td>.00 (-.05 to .05)</td>
<td>.991</td>
<td>-.01 (-.06 to .04)</td>
<td>.627</td>
</tr>
<tr>
<td>Morphine equivalent dose (per 50 mg/d)</td>
<td>.45 (.23 to .67)</td>
<td>&lt;.001</td>
<td>.28 (.07 to .49)</td>
<td>.008</td>
</tr>
</tbody>
</table>

* Adjusted for all other factors listed in the Table.

Hooten WM. Pain 2011;152:223
Where do opioids fit in?
Methadone & Cigarette Consumption

Chait LD. J Pharmacol Exp Ther 1984;229:636-40.
Schmitz JM. Drug Alcohol Depend 1994;34:237-42
Methadone & Cigarette Consumption

Methadone & Cigarette Consumption
Figure 1  Mean morphine equivalent dose (mg/d) at admission based on sex and smoking status.

* Two-way ANOVA, $F(2,621) = 8.8, P < 0.001.$

Hooten WM. Pain Med 2009;10:1416
Is there an association between smoking, opioid use and depression?
“...status as a current smoker was independently associated with greater opioid use, independent of depression.”

Hooten WM. Pain 2011;152:223
Hooten WM. Pain 2011;152:223

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>β Coefficient in univariate analysis (95% CI)</th>
<th>P value</th>
<th>β Coefficient in multivariate analysis* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>.00</td>
<td></td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>12.54 (-4.17 to 29.26)</td>
<td>.141</td>
<td>10.39 (-6.74 to 27.51)</td>
<td>.234</td>
</tr>
<tr>
<td>Current</td>
<td>30.44 (14.07 to 46.81)</td>
<td>&lt;.001</td>
<td>26.77 (9.11 to 44.44)</td>
<td>.003</td>
</tr>
<tr>
<td>CES-D score</td>
<td>.89 (.34 to 1.44)</td>
<td>&lt;.001</td>
<td>.38 (-.23 to .98)</td>
<td>.219</td>
</tr>
<tr>
<td>Age</td>
<td>2.04 (-1.21 to 5.25)</td>
<td>.115</td>
<td>1.43 (-.72 to 4.16)</td>
<td>.175</td>
</tr>
<tr>
<td>Female sex</td>
<td>-34.31 (-49.76 to -18.87)</td>
<td>&lt;.001</td>
<td>-32.99 (-48.96 to -17.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married</td>
<td>2.96 (-11.17 to 17.08)</td>
<td>.682</td>
<td>6.41 (-8.84 to 21.66)</td>
<td>.410</td>
</tr>
<tr>
<td>Years of education</td>
<td>-0.35 (-2.81 to 2.12)</td>
<td>.782</td>
<td>1.84 (-.73 to 4.42)</td>
<td>.160</td>
</tr>
<tr>
<td>Currently employed</td>
<td>-23.42 (-38.45 to -8.39)</td>
<td>.002</td>
<td>-19.97 (-35.70 to -4.24)</td>
<td>.013</td>
</tr>
<tr>
<td>Pain duration</td>
<td>.03 (-.60 to .67)</td>
<td>.919</td>
<td>.13 (-.54 to .79)</td>
<td>.707</td>
</tr>
<tr>
<td>Pain severity (per 50 mg/d)</td>
<td>1.45 (.74 to 2.17)</td>
<td>&lt;.001</td>
<td>1.09 (.29 to 1.90)</td>
<td>.008</td>
</tr>
</tbody>
</table>

* Adjusted for all other factors listed in the Table.
But does all this “stuff” help patients quit smoking?
Patient Beliefs and Attitudes

Smokers → Coping Strategy

Pain

Distress

Hooten WM. Pain Pract 2011;11:552
Patient Beliefs and Attitudes

Smokers → Opioid Use → Stimulated Smoking

Hooten WM. Pain Pract 2011;11:552
Physician Barriers to Providing Smoking Cessation Services

Physician

Knowledge

Time

Hooten WM. Pain Pract 2011;11:552
Smoking Cessation for Adults with Chronic Pain: A RCT
Smoking Cessation for Adults with Chronic Pain: A RCT
Smoking Cessation for Adults with Chronic Pain: A RCT

3-week time period
Smoking Cessation for Adults with Chronic Pain: A RCT

60 smokers

Intervention
N = 30
Quit
6 of 30

Control
N = 30
Quit
0 of 30

\[ P = 0.02 \]
Does pain improve after patients quit?
“Smoking cessation was not independently associated with changes in pain symptoms in older adults.”
Summary

Depression

Pain Severity

Smoking

Opioid Use