Smoking and Chronic Pain: Physiological and Clinical Correlations

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Disclosures

- None

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Objectives

- Discuss nicotinic and opioid receptor interactions
- Identify associations between smoking, opioid use and pain severity
- Discuss smoking cessation, chronic pain and treatment outcomes

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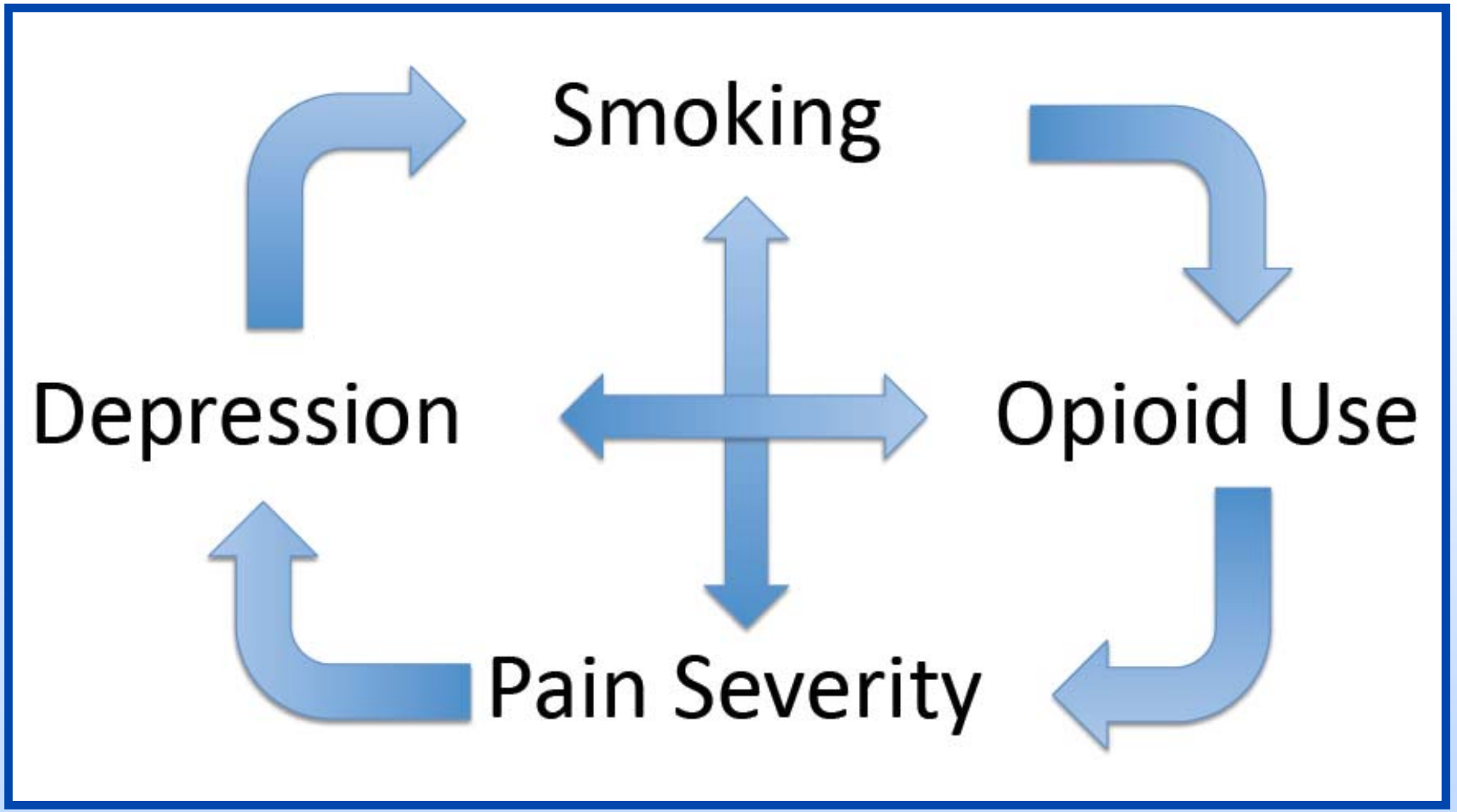

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After all these years, why are we still talking about smoking?

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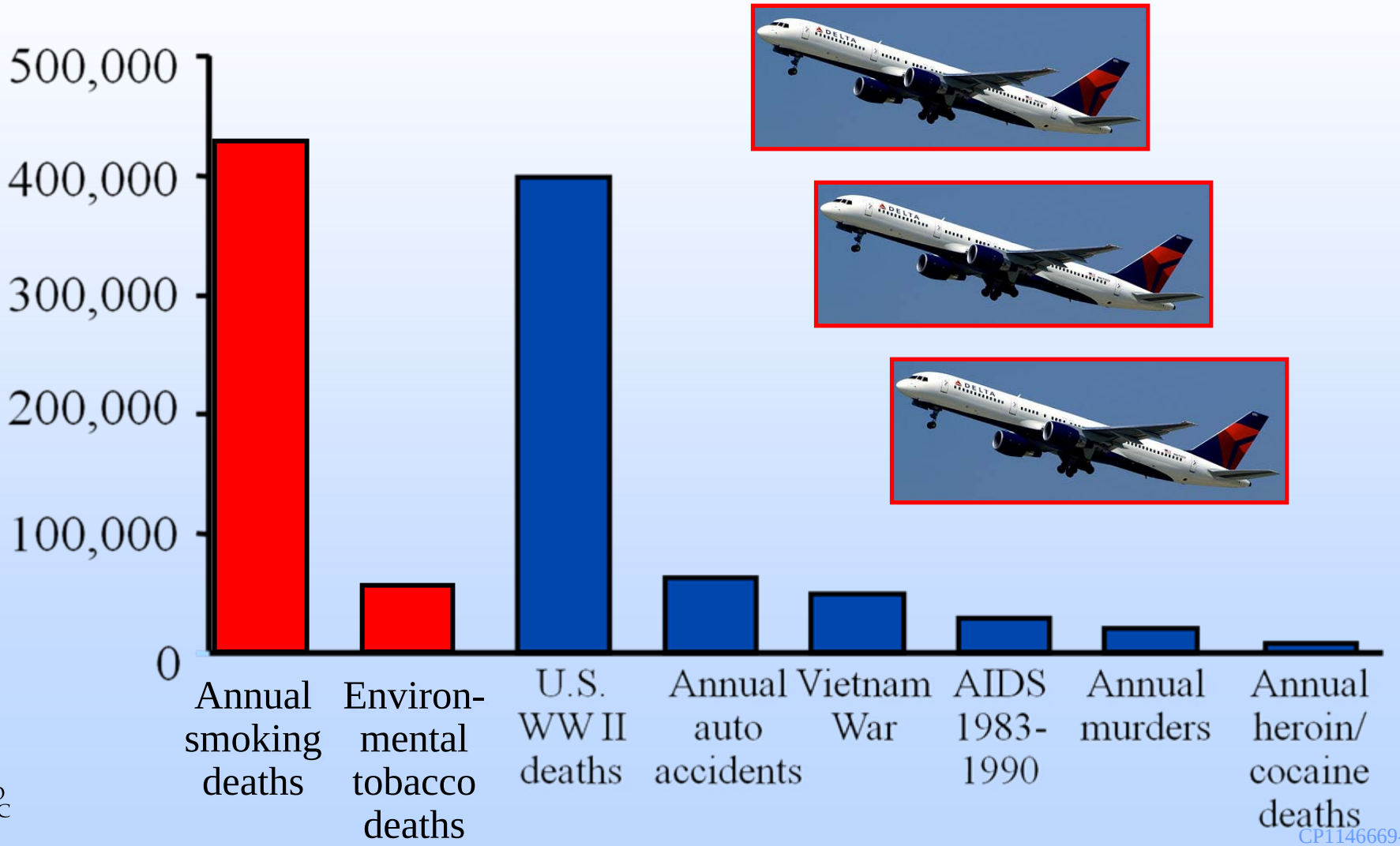
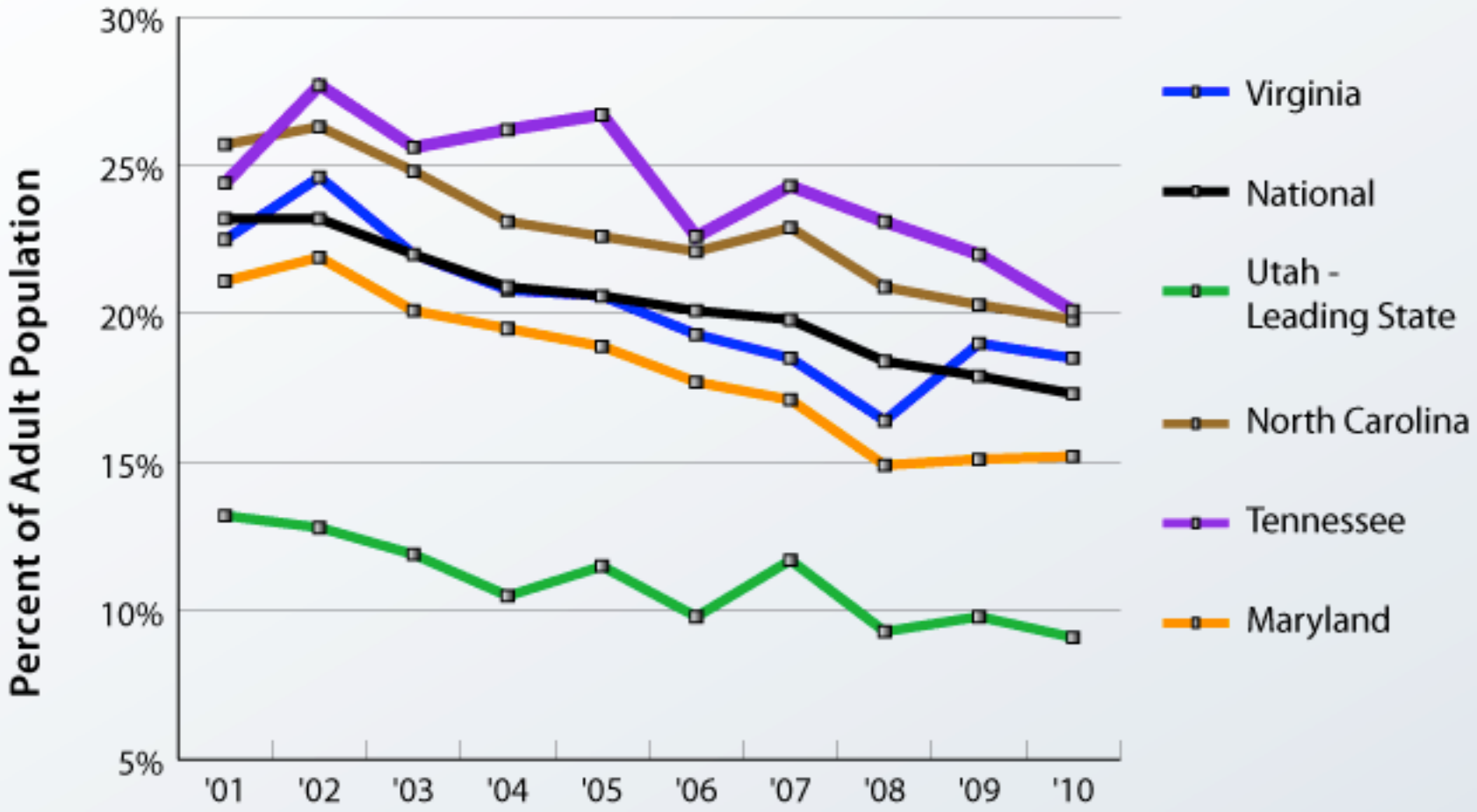
The Cigarette Death Epidemic in Perspective



Smoking Rate, By State



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Do we really need to talk about receptors?

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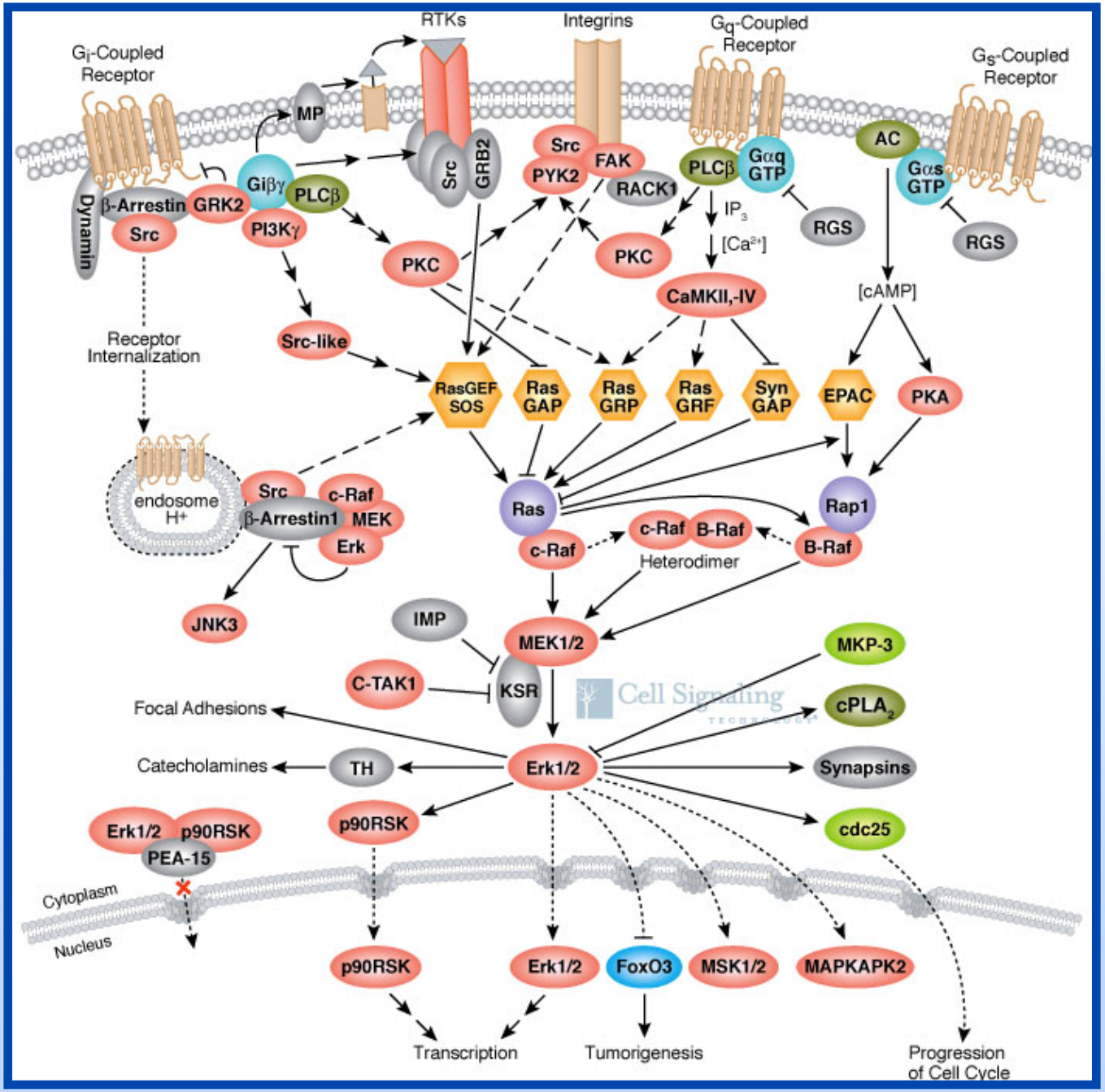
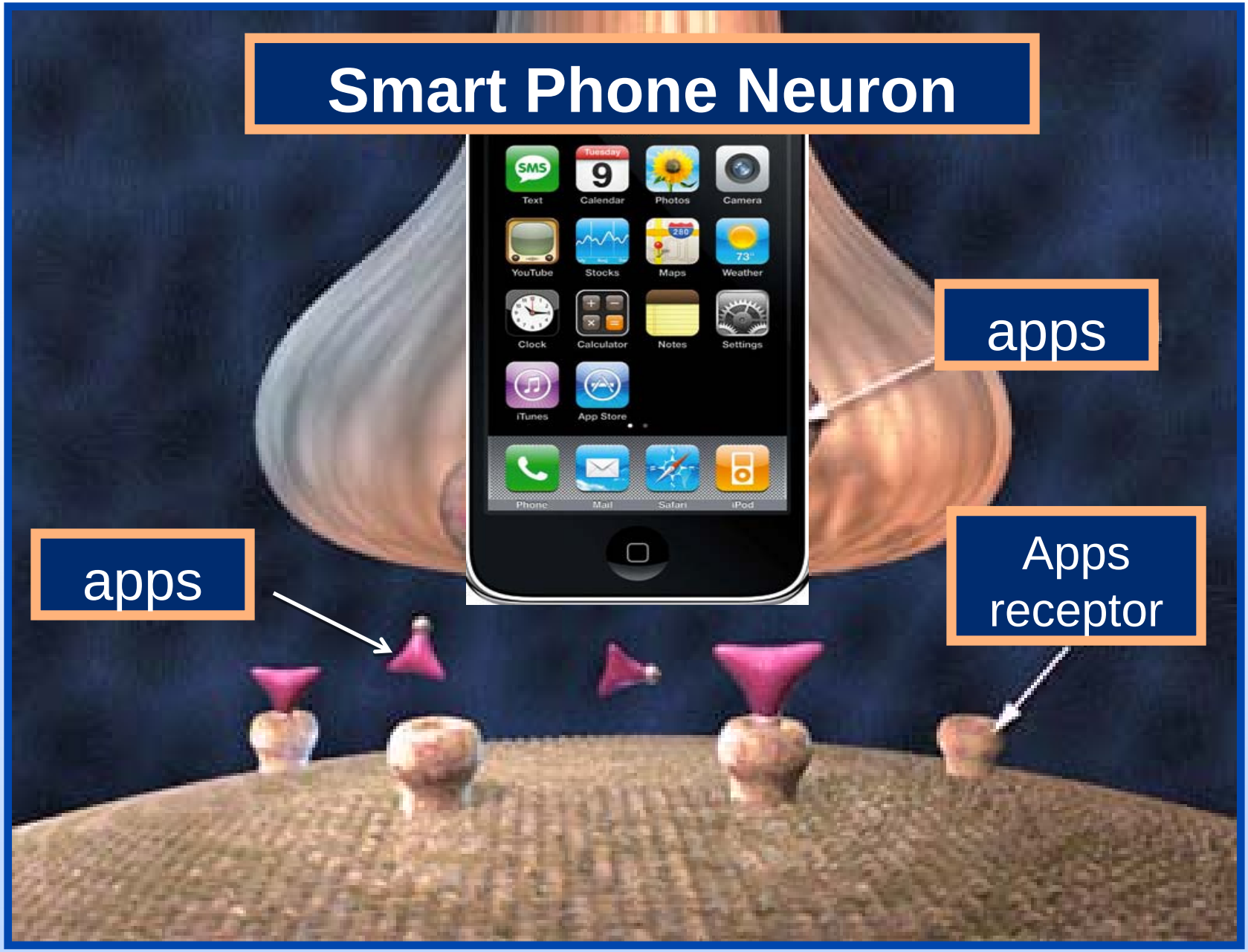
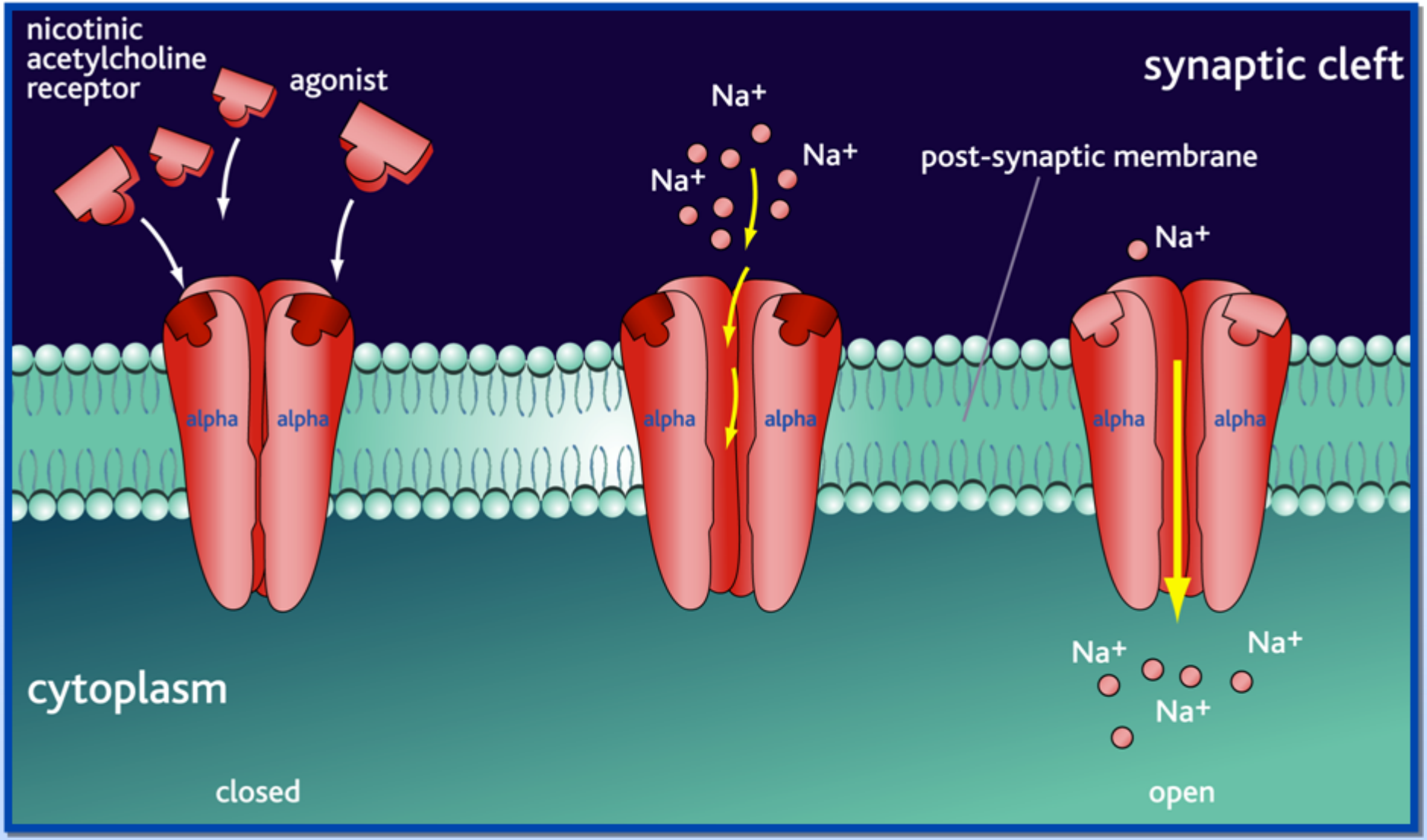
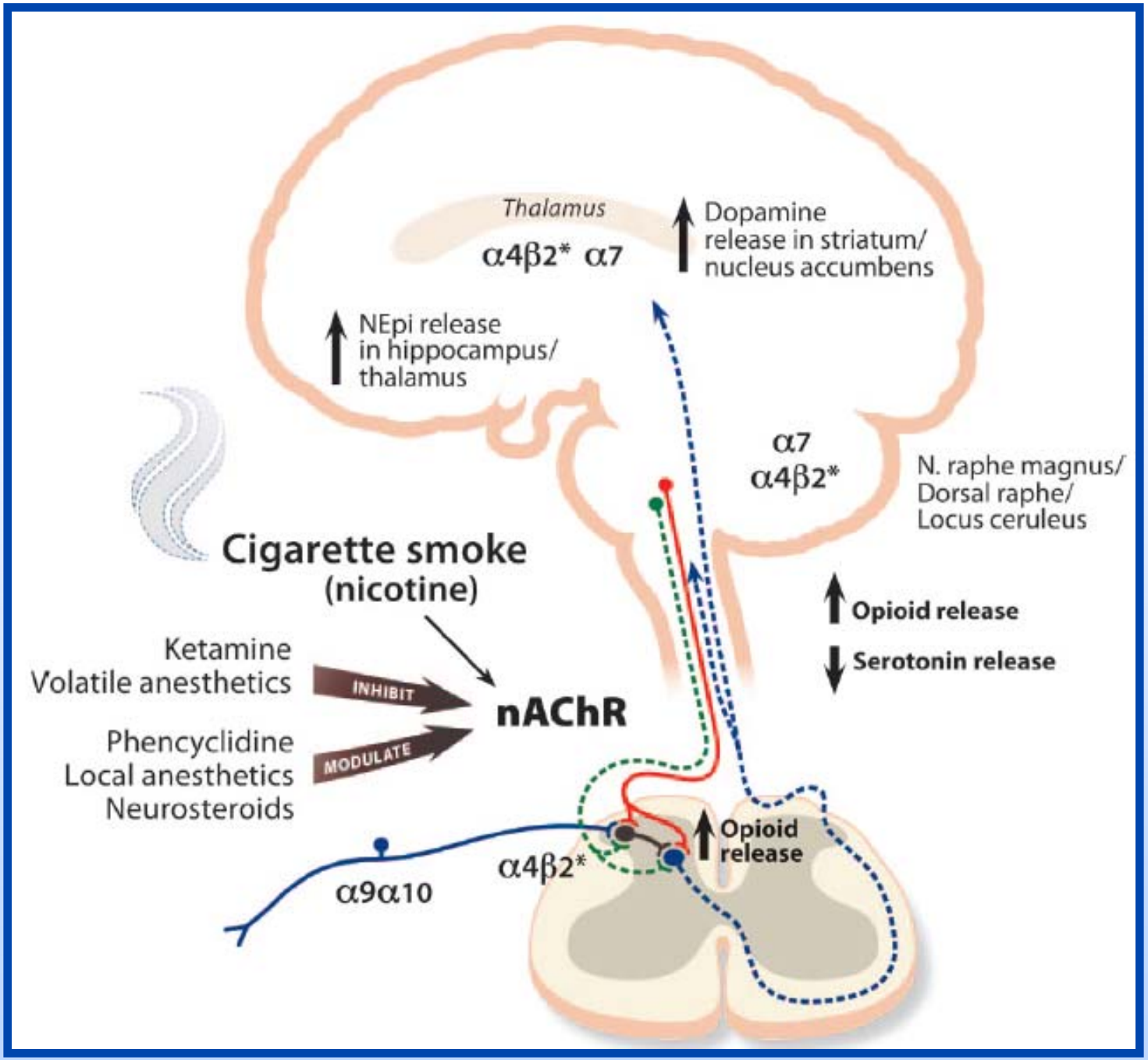

RTKs
Integrins
Gq-Coupled Receptor
Gi-Coupled Receptor
Gs-Coupled Receptor
MP
Src
GRB2
Src
FAK
PYK2
RACK1
PLCβ
Gαq GTP
AC
Gαs GTP
RGS
RGS
Dynamin
β-Arrestin
GRK2
Src
Giβγ
PLCβ
PI3Kγ
PKC
PKC
IP3
[Ca2+]
CaMKII,-IV
[cAMP]
Receptor Internalization
Src-like
RasGEF SOS
Ras GAP
Ras GRP
Ras GRF
Syn GAP
EPAC
PKA
endosome H+
Src
β-Arrestin1
c-Raf
MEK
Erk
Ras
Rap1
c-Raf
c-Raf
B-Raf
Heterodimer
B-Raf
JNK3
IMP
MEK1/2
MKP-3
C-TAK1
KSR
Cell Signaling TECHNOLOGY
cPLA2
Focal Adhesions
Catecholamines
TH
Erk1/2
Synapsins
Erk1/2
p90RSK
PEA-15
p90RSK
cdc25
Cytoplasm
Nucleus
p90RSK
Erk1/2
FoxO3
MSK1/2
MAPKAPK2
Transcription
Tumorigenesis
Progression of Cell Cycle

Smart Phone Neuron




nicotinic
acetylcholine
receptor
agonist
synaptic cleft
Na+
Na+
Na+
post-synaptic membrane
Na+
alpha
alpha
alpha
alpha
alpha
alpha
cytoplasm
Na+
Na+
Na+
closed
open


Thalamus
α4β2* α7
Dopamine release in striatum/ nucleus accumbens
NEpi release in hippocampus/ thalamus
α7
α4β2*
N. raphe magnus/ Dorsal raphe/ Locus ceruleus
Cigarette smoke (nicotine)
Opioid release
Serotonin release
Ketamine
Volatile anesthetics
INHIBIT
nAChR
Phencyclidine
Local anesthetics
Neurosteroids
MODULATE
Opioid release
α4β2*
α9α10

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

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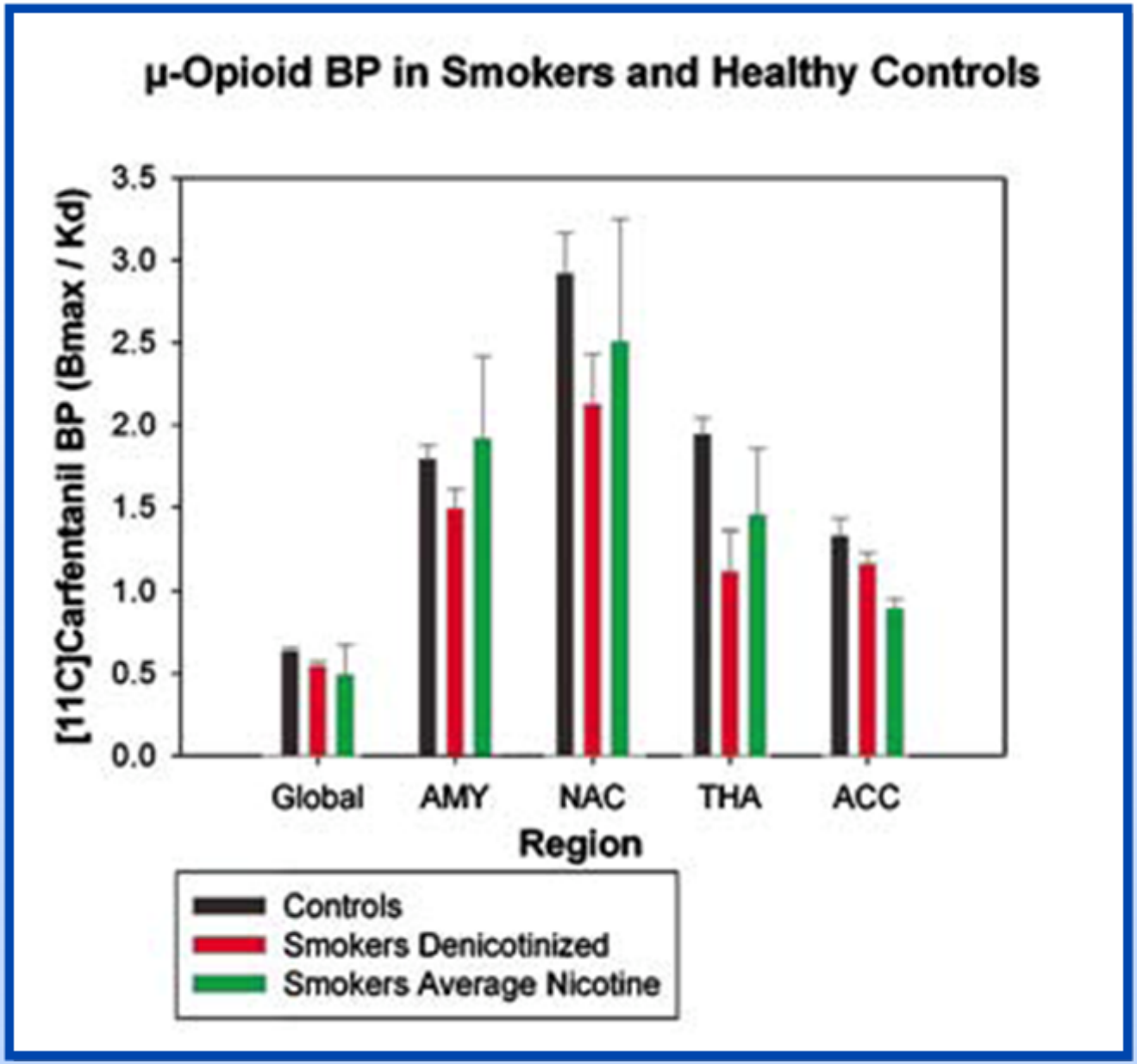

Scott DJ. Neuropsychopharmacology 2007;32:450-7

Does smoking cause chronic pain?

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Leboeuf-Yde C. Spine 1999;24:1463-70.

"...smoking…considered to be a weak risk indicator and not a risk factor for chronic low back pain."

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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

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PAIN® 151 (2010) 366–371

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www.elsevier.com/locate/pain

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

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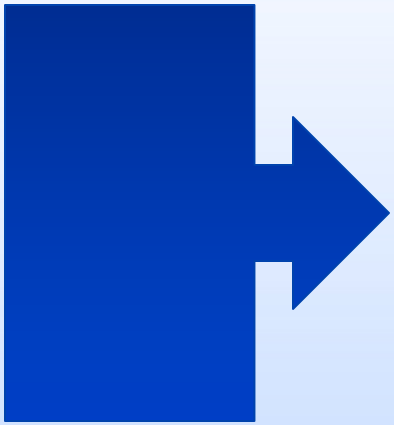
Depression

Overweight



Pain

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Smoking  Pain

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"…smoking increased the likelihood of incident pain only among subjects who reported depression."

Do smokers have greater pain severity?

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Smoking

Pain Severity

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Comparison between Smokers and Nonsmokers

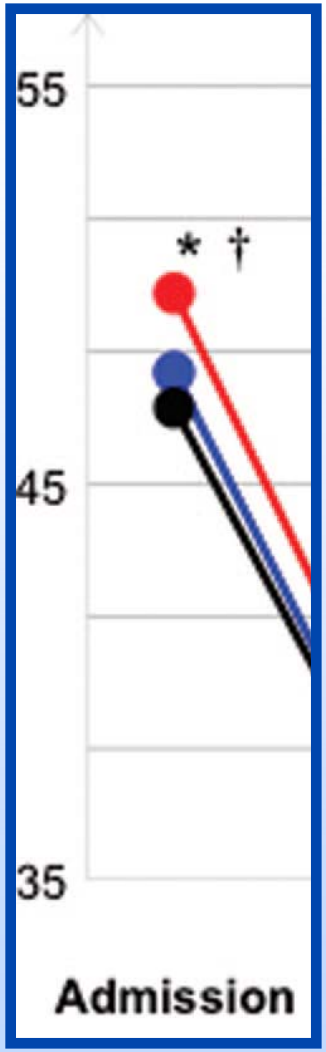
Study	Year	Subjects: Smoking Status	Subjects: Smoker+ Nonsmoker: Male	Subjects: Smoker+ Nonsmoker: Female	Painful Stimulus: Cold Pressor	Painful Stimulus: Electrical	Painful Stimulus: Thermal Heat	Painful Stimulus: Thermal Ischemia
Silverstein[149]	1982	Deprived	38 + 13			Th −		
Perkins[108]	1994	Deprived	10 + 10				Th −	
		Deprived	6 + 6	6 + 6			Th 0	
		Deprived	9 + 9	9 + 9			Th 0	
Jamner[10]	1998	Deprived	17 + 13	21 + 23		Th +, T + (males only)		
Girdler[118]	2005	Not deprived	20 + 20	17 + 20	Th +, T + (males only)		Th 0, T 0	Th +, T + (females only)

"Deprived" smokers were abstinent 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

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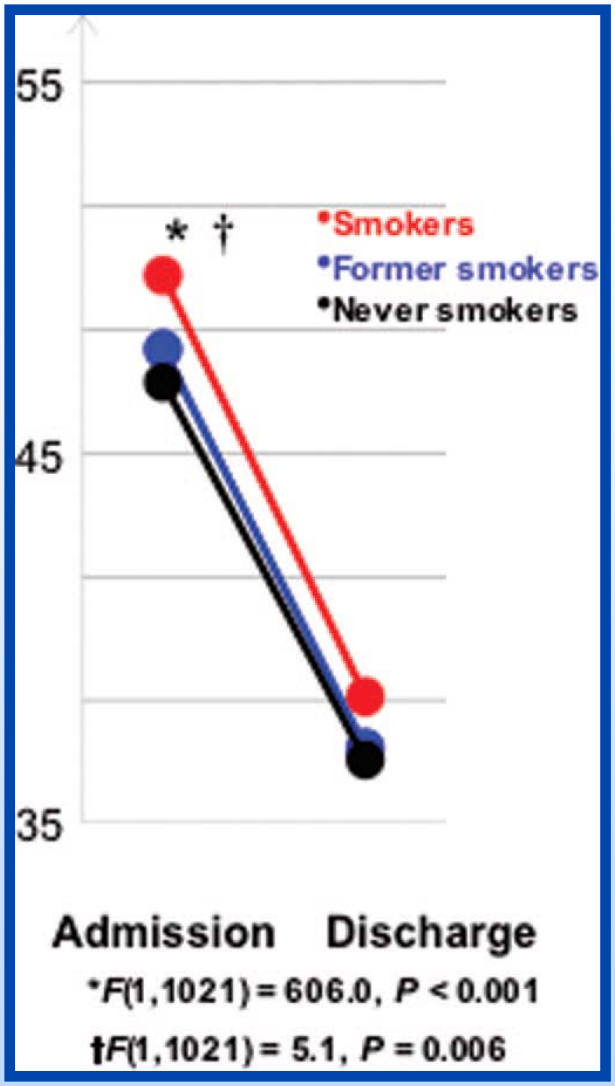
Effects of Smoking Status on Pain Severity



Hooten WM. Anesthesia & Analgesia 2009;108:308

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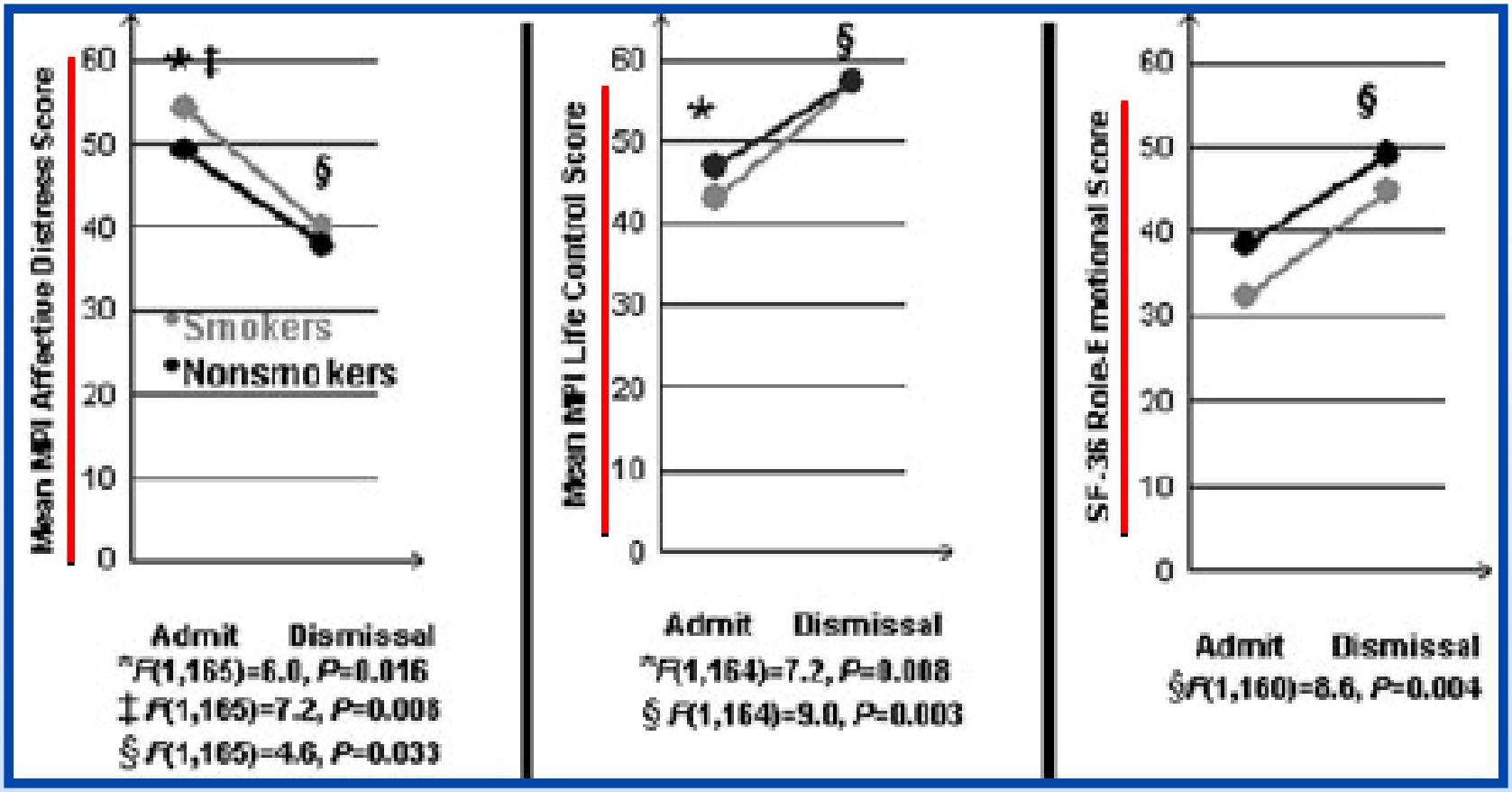
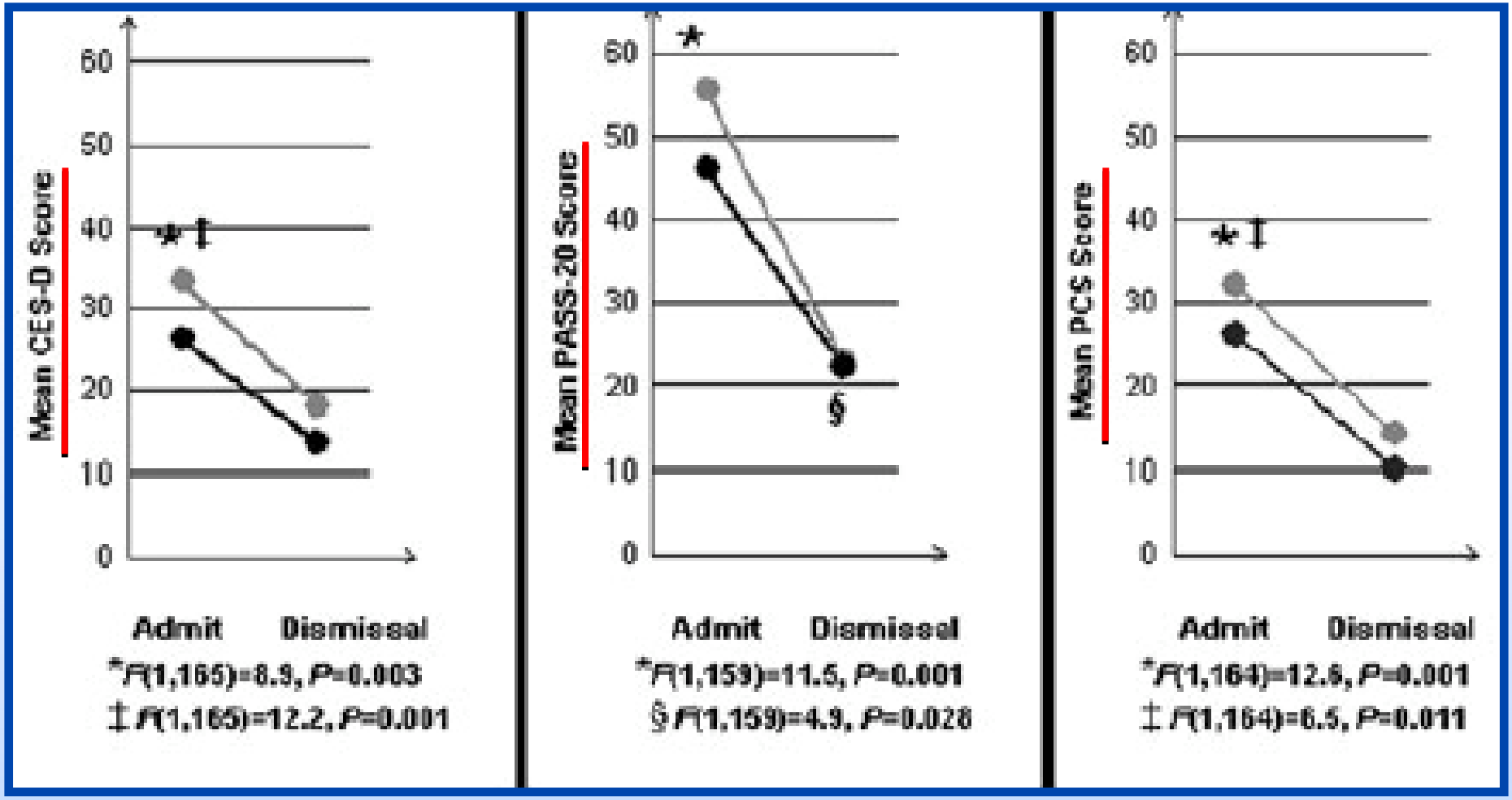


* Main effect of time, repeated measures ANCOVA.

‡ Main effect of smoking status, repeated measures ANCOVA.

§ Interaction of time and smoking status, repeated measures ANCOVA.

Hooten WM. Pain Med 2009;10:347



* Main effect of time, repeated measures ANCOVA.
‡ Main effect of smoking status, repeated measures ANCOVA.
§ Interaction of time and smoking status, repeated measures ANCOVA.

Hooten WM. Pain Med 2009;10:347

What about the potential effects of depression?

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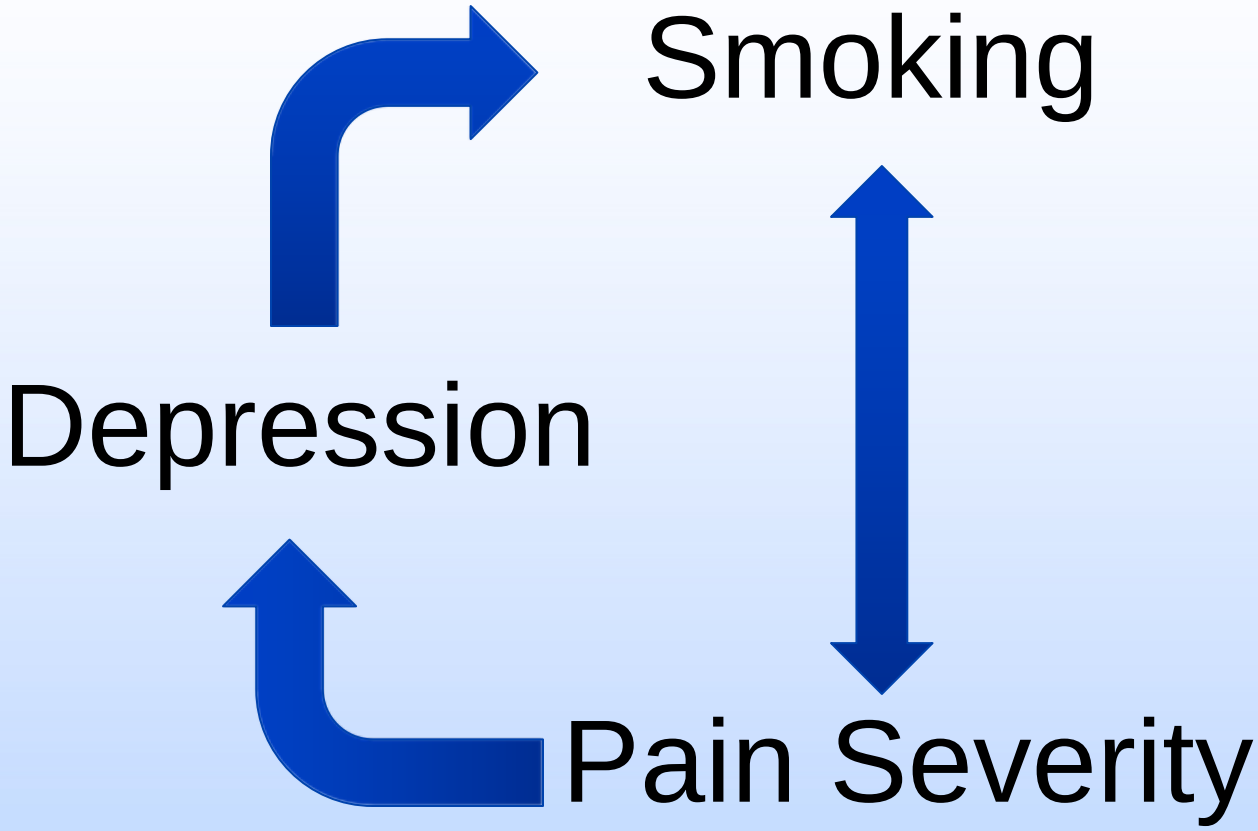

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Depression → Chronic Pain

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Chronic Pain  Depression

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Chronic Pain  Depression

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A.

Depression  Chronic Pain

B.

Depression  Pain Severity

C.

Depression  Smoking

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PAIN® 152 (2011) 223–229

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www.elsevier.com/locate/pain

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.

Variable	Current smoker ($n = 313$)	Former smoker ($n = 294$)	Never smoker ($n = 634$)	P value*
CES-D				
Baseline	30.2 ± 12.5[a,**]	26.1 ± 11.9[b]	25.0 ± 12.2[b]	<.001
MPI pain severity				
Baseline	49.8 ± 9.8[a]	47.8 ± 9.0[b]	46.9 ± 9.4[b]	<.001

* 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

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"…baseline pain severity was independently associated with greater levels of depression, but not with smoking status."

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Linear regression analyses with baseline MPI pain severity as the outcome variable.

	β Coefficient in univariate analysis (95% CI)	*P* value	β Coefficient in multivariate analysis* (95% CI)	*P* value
Smoking status				
Never	.00		.00	
Former	.86 (−.45 to 2.18)	.197	−.06 (−1.29 to 1.17)	.922
Current	2.89 (1.58 to 4.20)	<.001	.51 (−.76 to 1.78)	.427
CES-D score	.28 (.23 to .31)	<.001	.25 (.21 to .29)	<.001
Age	.03 (−.01 to .07)	.156	.06 (.02 to .10)	.002
Female sex	−.45 (−1.70 to .79)	.474	−.41 (−1.56 to .74)	.485
Married	−.74 (−1.87 to .39)	.201	−.83 (−1.92 to .26)	.137
Years of education	−.69 (−.89 to −.50)	<.001	−.53 (−.71 to −.34)	<.001
Currently employed	−4.45 (−5.62 to −3.29)	<.001	−2.72 (−3.84 to −1.60)	<.001
Pain duration	.00 (−.05 to .05)	.991	−.01 (−.06 to .04)	.627
Morphine equivalent dose (per 50 mg/d)	.45 (.23 to .67)	<.001	.28 (.07 to .49)	.008

* Adjusted for all other factors listed in the Table.

Hooten WM. Pain 2011;152:223

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Where do opioids fit in?

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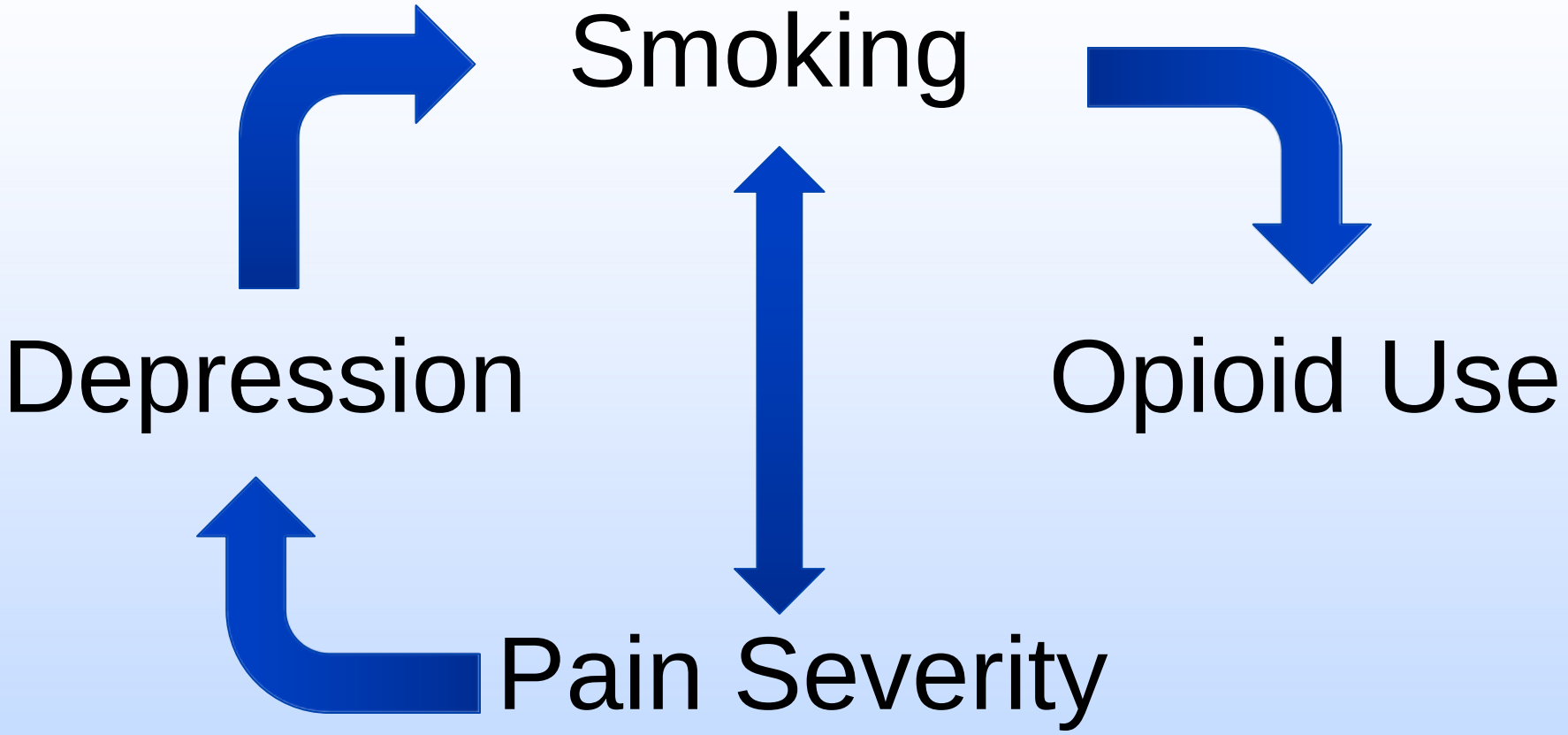

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Methadone & Cigarette Consumption

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

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Methadone & Cigarette Consumption

Spiga R. Drug Alcohol Depend 1998;50:157-65

Methadone & Cigarette Consumption

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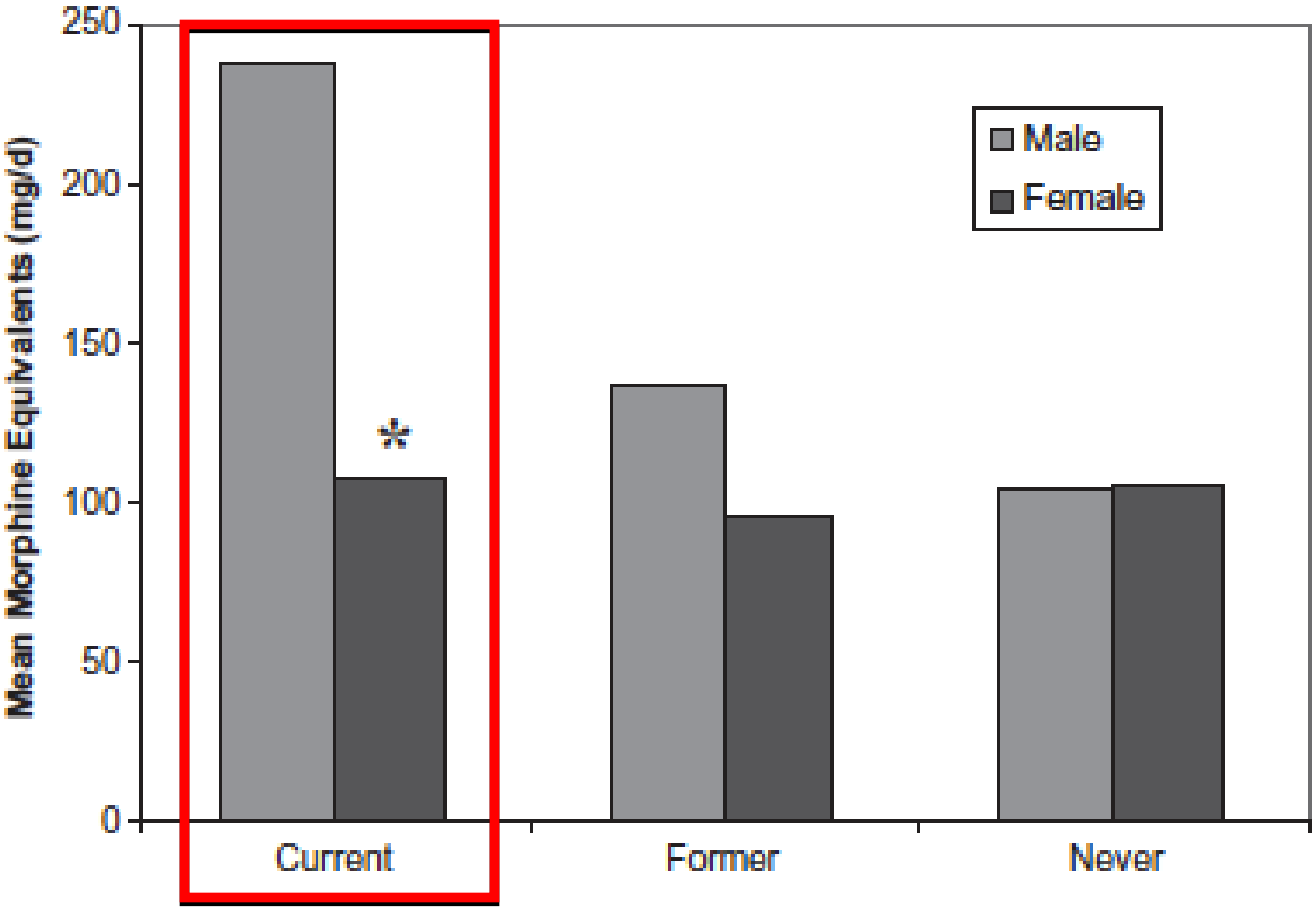

Figure 1 Mean morphine equivalent dose (mg/d) at admission based on sex and smoking status.
* Two-way ANOVA, $F(2,621) = 8.8$, $P < 0.001$.

Hooten WM. Pain Med 2009;10:1416

Is there an association between smoking, opioid use and depression?

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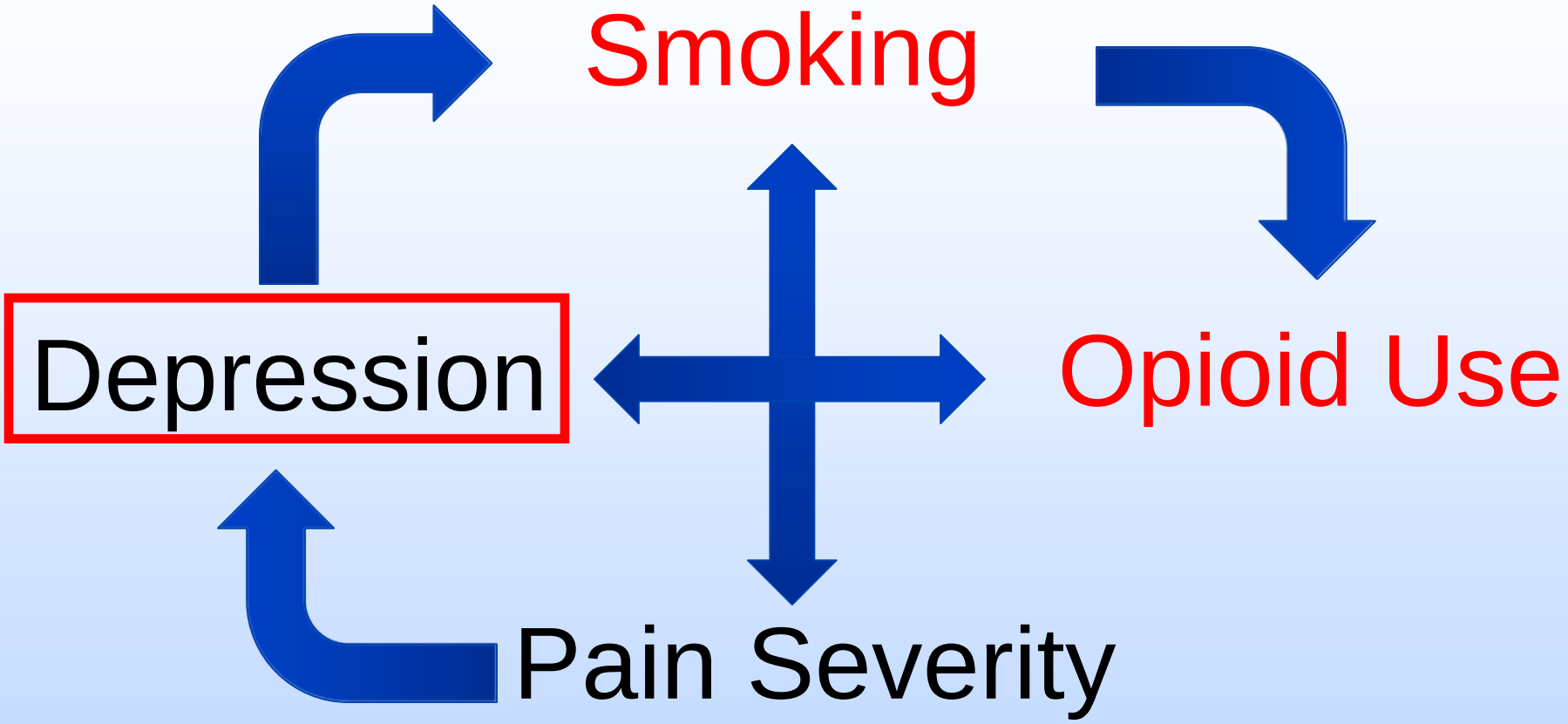

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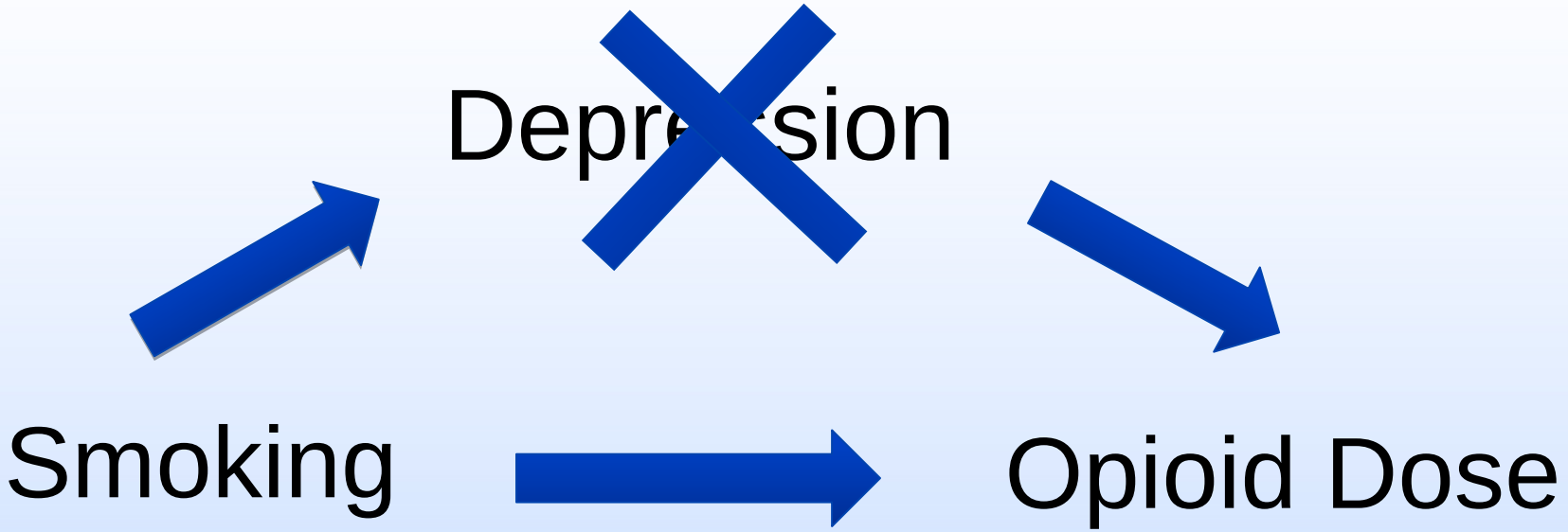

"…status as a current smoker was independently associated with greater opioid use, independent of depression."

Hooten WM. Pain 2011;152:223

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Linear regression analyses with baseline morphine equivalent dose as the outcome variable.

	β Coefficient in univariate analysis (95% CI)	*P* value	β Coefficient in multivariate analysis* (95% CI)	*P* value
Smoking status				
Never	.00		.00	
Former	12.54 (−4.17 to 29.26)	.141	10.39 (−6.74 to 27.51)	.234
Current	30.44 (14.07 to 46.81)	<.001	26.77 (9.11 to 44.44)	.003
CES-D score	.89 (.34 to 1.44)	<.001	.38 (−.23 to .98)	.219
Age	[illegible]	[illegible]	[illegible]	[illegible]
Female sex	−34.31 (−49.76 to −18.87)	<.001	−32.99 (−48.96 to −17.01)	<.001
Married	2.96 (−11.17 to 17.08)	.682	6.41 (−8.84 to 21.66)	.410
Years of education	−.35 (−2.81 to 2.12)	.782	1.84 (−.73 to 4.42)	.160
Currently employed	−23.42 (−38.45 to −8.39)	.002	−19.97 (−35.70 to −4.24)	.013
Pain duration	.03 (−.60 to .67)	.919	.13 (−.54 to .79)	.707
Pain severity (per 50 mg/d)	1.45 (.74 to 2.17)	<.001	1.09 (.29 to 1.90)	.008

* Adjusted for all other factors listed in the Table.

Hooten WM. Pain 2011;152:223

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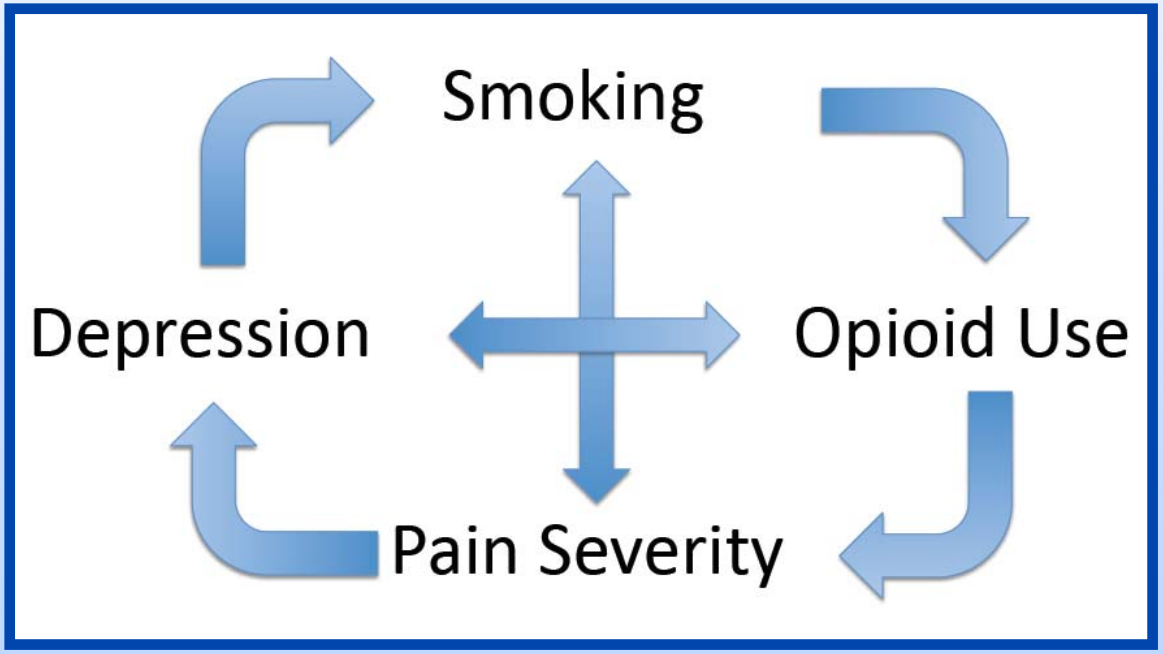
But does all this “stuff” help patients quit smoking?



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Patient Beliefs and Attitudes

Hooten WM. Pain Pract 2011;11:552

Patient Beliefs and Attitudes

Smokers → Opioid Use → Stimulated Smoking

Hooten WM. Pain Pract 2011;11:552

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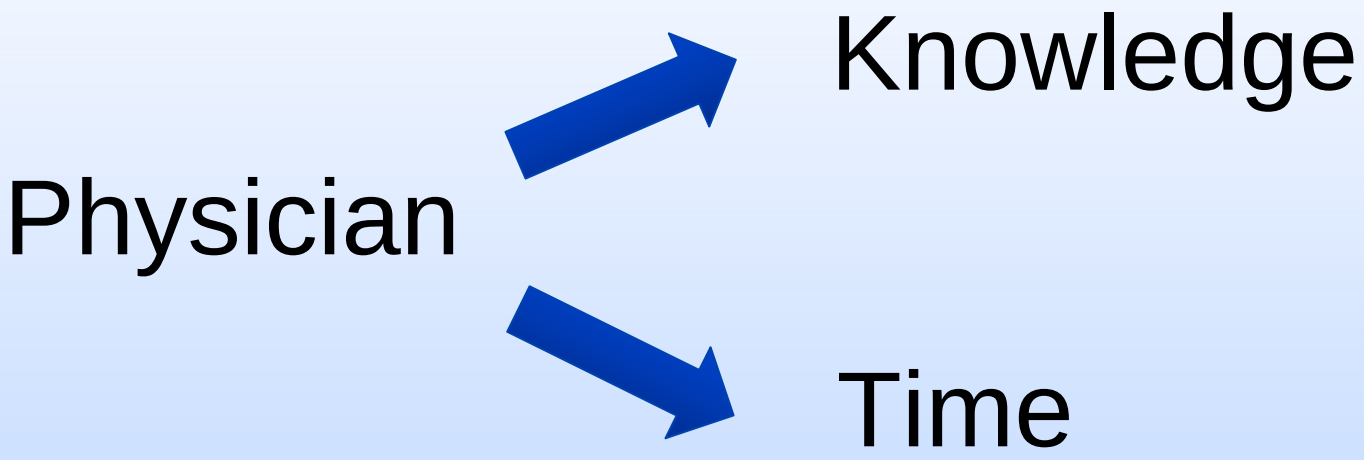
Physician Barriers to Providing Smoking Cessation Services



Hooten WM. Pain Pract 2011;11:552

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Smoking Cessation for Adults with Chronic Pain: A RCT

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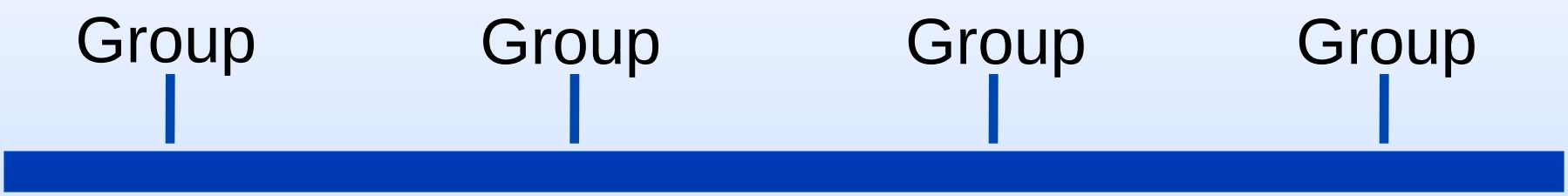
Smoking Cessation for Adults with Chronic Pain: A RCT



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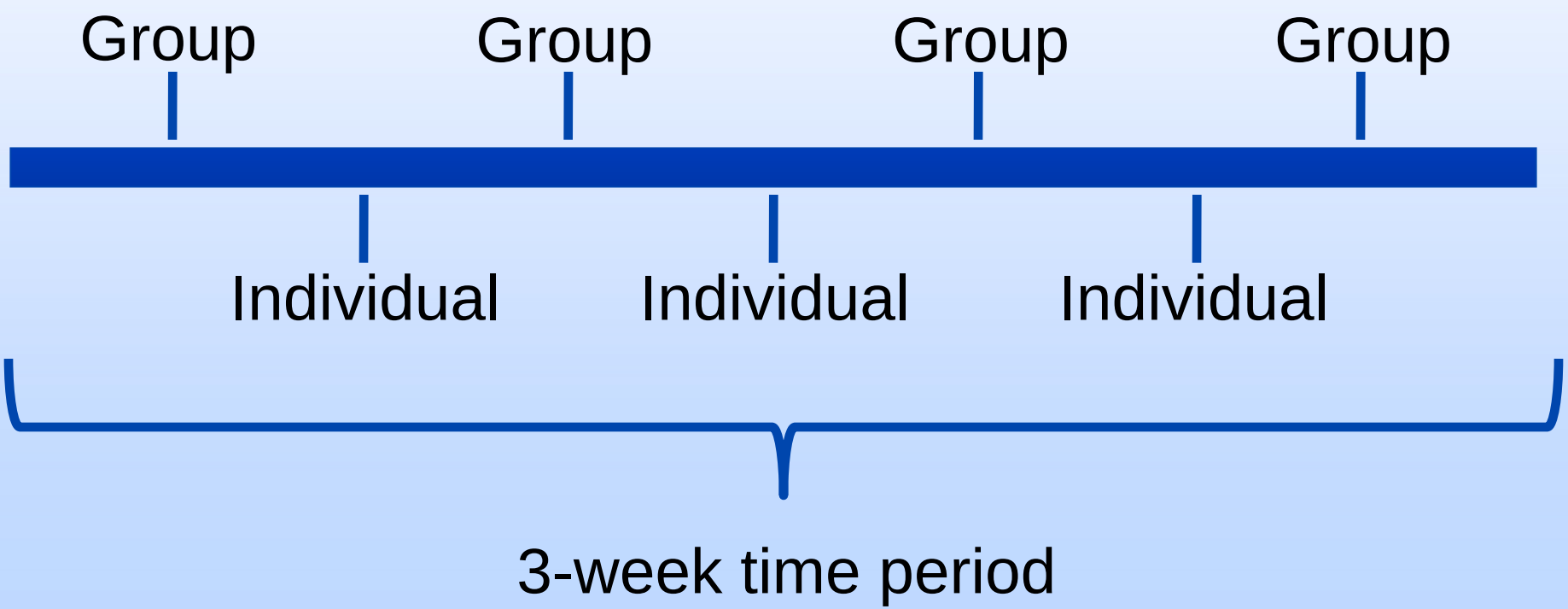
Smoking Cessation for Adults with Chronic Pain: A RCT



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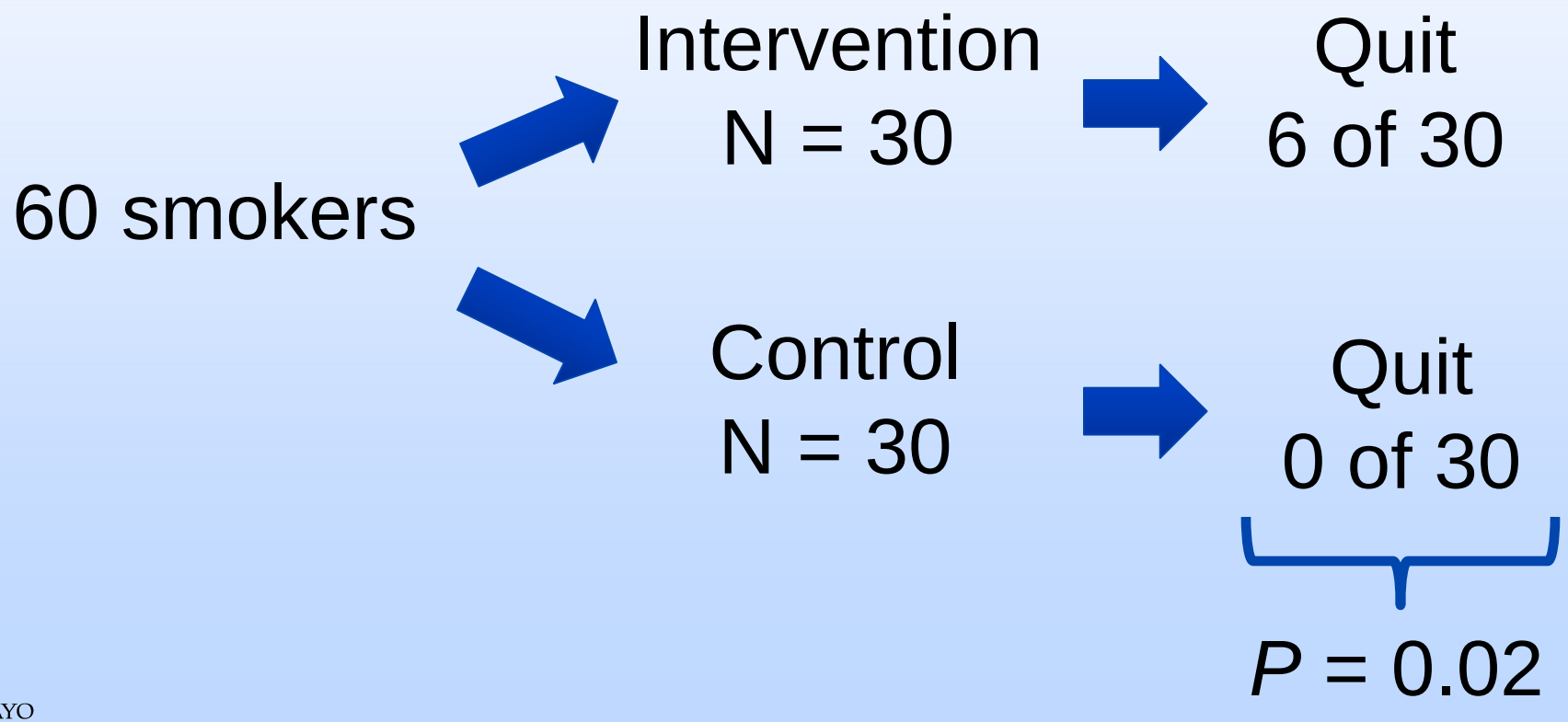
Smoking Cessation for Adults with Chronic Pain: A RCT



Does pain improve after patients quit?

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Nicotine & Tobacco Research, Volume 13, Number 10 (October 2011) 919–925

Original Investigation

Effects of Smoking Cessation on Pain in Older Adults

Yu Shi, M.D., M.P.H.,[1,2] *W. Michael Hooten, M.D.,*[1,2] *& David O. Warner, M.D.*[1,2]

"Smoking cessation was not independently associated with changes in pain symptoms in older adults."

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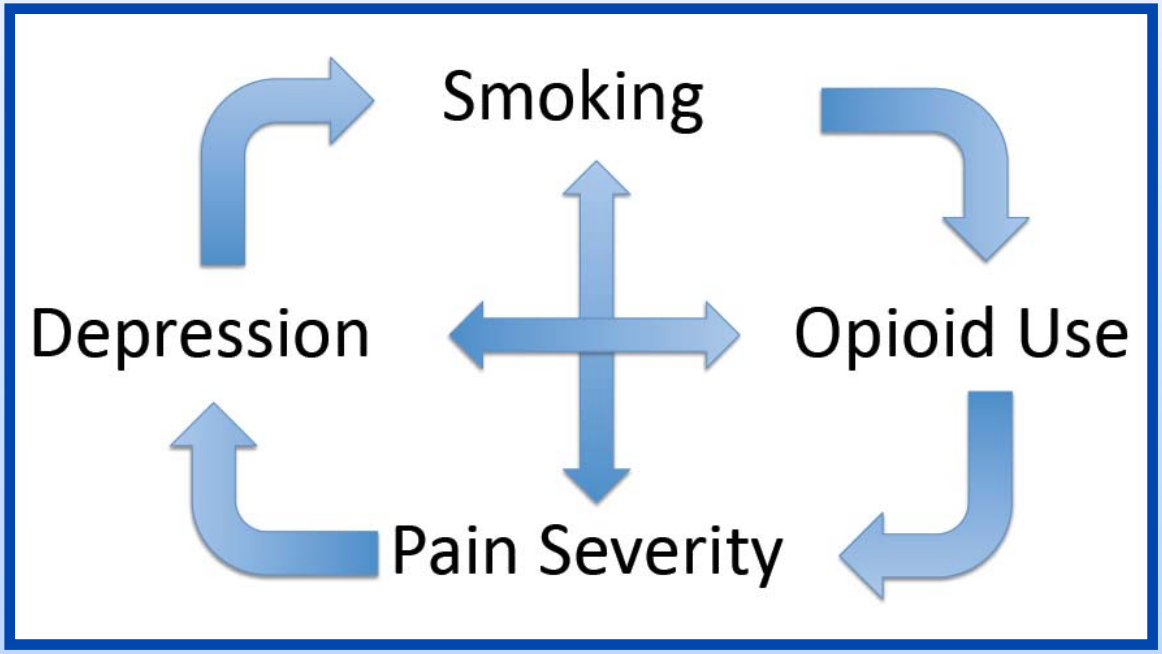
Summary



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Questions & Discussion