Anesthesiology 2010; 113:977–92

Smoking and Pain

Pathophysiology and Clinical Implications

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ABSTRACT

Cigarette smoke, which serves as a nicotine delivery vehicle in humans, produces profound changes in physiology. Experimental studies suggest that nicotine has analgesic properties. However, epidemiologic evidence shows that smoking is a risk factor for chronic pain. The complex relationship between smoking and pain not only is of scientific interest, but also has clinical relevance in the practice of anesthesiology and pain medicine. This review will examine current knowledge regarding how acute and chronic exposure to nicotine and cigarette smoke affects acute and chronic painful conditions. It will cover the relevant pharmacology of nicotine and other ligands at the nicotinic acetylcholine receptor as related to pain, explore the association of cigarette smoking with chronic painful conditions and potential mechanisms to explain this association, and examine clinical implications for the care of smokers with pain.

APPROXIMATELY 1 in 5 Americans smoke cigarettes,[1] and at least 1 in 10 nonsmokers is exposed to secondhand smoke at home.[2] Thus a large population is chronically exposed to nicotine and the other constituents of cigarette smoke. The implications of cigarette smoking to the practice of anesthesiology and pain medicine are complex and not well understood. Cigarette smoke contains thousands of compounds, with many of them producing significant physiologic effects. However, cigarettes serve primarily as a device to deliver nicotine. Nicotine has analgesic properties, first observed in feline visceral pain models[3] and since then replicated in numerous animal and human studies.[4–13] Its analgesic effects likely result from effects at both central and peripheral nicotine acetylcholine receptors (nAChRs).[8,14,15] Other nAChR ligands also have potent analgesic effects.[16–20] On the other hand, clinical evidence suggests that smokers are at increased risk of developing back pain and other chronic pain disorders.[21–32] Furthermore, comparisons between smokers and nonsmokers with chronic pain disorders have repeatedly demonstrated that smokers have higher pain intensity scores that have greater impact on occupational and social function.[33–37] This apparent paradox is not only of considerable scientific interest, but also has clinical relevance in caring for smokers in the perioperative period and smokers with chronic painful conditions.

This paper will review how acute and chronic exposure to nicotine, which is currently delivered most commonly *via* cigarette smoke, affects acute and chronic painful conditions. We first review briefly the relevant pharmacology of nicotine and other ligands at the nAChR as related to pain, explore the association of cigarette smoking with chronic painful conditions and potential mechanisms to explain this association, and examine clinical implications for those who care for smokers with pain. We focus on cigarette smoking, as most of the relevant literature in humans concerns this method of nicotine delivery, recognizing that other forms of tobacco use (*e.g.*, smokeless tobacco) may have similar (or different) effects on pain.

Pharmacology of Nicotine Acetylcholine Receptors

The alkaloid nicotine exhibits its pharmacological effects by interacting with ion channels of the nAChR family. The nAChR consists of a pentameric complex of transmembrane proteins that form a central pore permeable to Na^+, Ca^{2+}, and K^+ ions.[38] The structure of the muscle-type of nAChR has been characterized with high resolution and has served for modeling ligand binding sites of neuronal nAChRs.[39]

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Received from the Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota. Submitted for publication February 8, 2010. Accepted for publication April 15, 2010. Support was provided solely from institutional and/or departmental sources. The figures in this article were prepared by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

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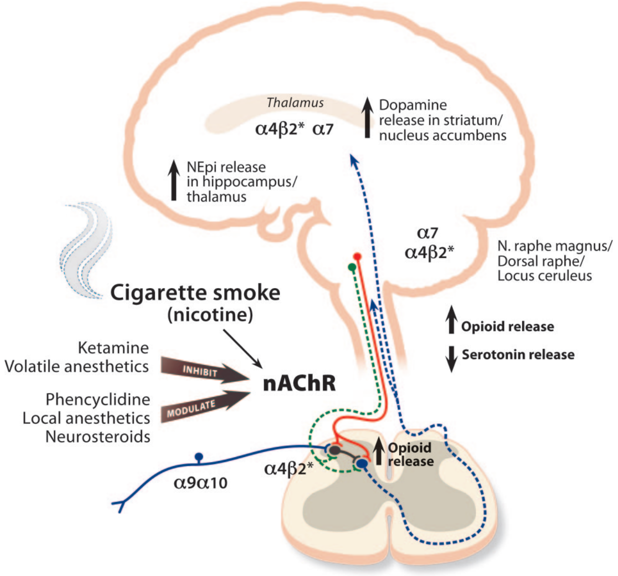

Fig. 1. Schematic representation of the potential sites of analgesic action of nicotine. In the central nervous system, there is widespread distribution of homomeric $\alpha7$ and heteromeric $\alpha4\beta2^*$ nicotinic acethylcholine receptors (nAChR), including regions associated with pain transmission such as the dorsal horn, locus ceruleus, and thalamus. The $\alpha9\alpha10$ nAChR is present in dorsal root ganglia. Many anesthetics also modulate or inhibit nAChR function. Activation of supraspinal and spinal nAChR results in opioid and norepinephrine (NEpi) release, which can reduce descending facilitatory pain pathways (*green*) and enhance descending inhibitory pain pathways (*red*), resulting in reduced transmission of nociceptive input (*blue*).

Muscle-type nAChRs consist of $(\alpha1)_2\beta1\delta\varepsilon$ (adult) or $(\alpha1)_2\beta1\delta\gamma$ (fetal) forms, with $\alpha1$, $\beta1$, γ, δ, and ε subunits being expressed only in skeletal muscle. Neuronal nAChRs are composed of different combinations of α ($\alpha2$–$\alpha10$) and non-α ($\beta2$–$\beta4$) subunits.[40] The endogenous ligand ACh binds at the interface between an α subunit and neighboring subunits, and thus, nAChRs will differ in their ACh binding depending on their subunit composition. Whereas $\alpha4\beta2^*$ heteromers (where * denotes possible additional subunits) will have two binding sites for agonists and competitive antagonists, homopentameric $\alpha7$ nAChRs will have up to five binding sites.[38,41]

The family of nAChRs shows wide distribution in the central and peripheral nervous systems and is involved in numerous processes, including arousal, sleep, anxiety, cognition, and pain.[38] In the central nervous system, the homomeric $\alpha7$ (α-bungarotoxin-sensitive) and the heteromeric $\alpha4\beta2^*$ (α-bungarotoxin-insensitive) receptors predominate.[42–44] The $\alpha4\beta2^*$ receptors are present in the spinal cord dorsal horn, thalamus, and other brain regions associated with nociceptive transmission and modulation.[45,46] The $\alpha9\alpha10$ nAChR (also α-bungarotoxin-sensitive) is not present in the central nervous system, but is found in the dorsal root ganglia, leukocytes, vestibular and cochlear mechanosensory hair cells, and other tissues[47–49](fig. 1).

Activation of postsynaptic nAChRs exerts direct excitatory neuronal effects *via* their cationic channel. Presynaptically, nAChR activation can potentiate the release of other neurotransmitters, including dopamine, γ-aminobutyric acid, glutamate, serotonin, histamine, and norepinephrine.[38,40] Subsequent neurotransmitter release contributes to the complex effects of nicotine and other nAChR ligands in different neuronal pathways. Neuronal nAChRs have multiple ligands and modulators, including neurosteroids, local anesthetics, phencyclidine, and MK-801.[50] Volatile anesthetics and ketamine are potent inhibitors of $\alpha4\beta2$ and $\alpha3\beta4$ nAChRs at clinically relevant doses.[51] Particular nAChR subunits exhibit varying selectivity to the different ligands, thus contributing to complex pharmacological profiles. In addition, the kinetics of nAChR channel opening may vary. Whereas nAChRs display fast opening of their cation channel upon ACh binding in response to the usual high-concentration, brief exposure to released ACh, when they are exposed chronically to low agonist concentrations, there is a reduction in channel opening rates, resulting in a closed, desensitized state.[38] During prolonged exposure to nAChR ligands, changes in receptor number or function may occur. For instance, prolonged exposure of animals to low levels of nicotine typically seen in chronic smokers results in an up to 2-fold up-regulation of nAChR expression in the brain.[52,53] Human studies using positron emission tomography also show that smokers have greater densities of high-affinity AChRs in several brain regions compared with nonsmokers and ex-smokers.[54] These aspects of nAChR pharmacology are clearly important in drug development. In the following section, nAChR ligands investigated in animal models and human studies in regard to pain behaviors and perception are considered.

Animal Studies

Nicotine. In 1932, Davis *et al.* reported that systemic nicotine attenuated pain behaviors in an experimental visceral pain model of gallbladder distention in cats.[3] Subsequent work demonstrated that although activation of peripheral nAChRs produces pain,[55,56] acute exposure to systemic nicotine has consistent antinociceptive effects in rodents as measured in tail flick and hot plate models.[4–8,57,58] For example, Tripathi demonstrated that subcutaneous administration of nicotine produced a significant increase in tail flick test thresholds in both male rats (1 mg/kg) and mice (3 mg/kg).[8] Different pain models may involve different neural pathways,[59] and nicotine does not consistently have similar effects in thermal paw withdrawal or mechanical pain models (Von Frey tests),[57,58] although such effects are present in a mouse model of postoperative pain.[60] The antinociceptive properties of nicotine are also evident when nicotine is administered *via* cigarette smoke.[57,61]

Several possible mechanisms may be involved in the antinociceptive properties of systemic nicotine. Withdrawal reflexes are spinally mediated but also modulated supraspinally,[62] so that activation of nAChRs at both spinal and supraspinal sites may be involved; studies using systemic treatments cannot elucidate the effect site. A supraspinal site for the antinociceptive effects of nicotine is suggested by the involvement of opioid and serotonergic systems (fig. 1).

Several lines of evidence suggest that the antinociceptive properties of nicotine are at least partly mediated by the endogenous opioid system. First, the antinociceptive effects of nicotine on the tail flick test are blocked by the administration of either the centrally acting nicotinic antagonist mecamylamine or the opioid antagonist naltrexone.[61] Berrendero *et al.* demonstrated that nicotine antinociception is attenuated in μ-opioid receptor knock-out mice and in mice that lack the preproenkephalin gene.[63,64] Second, centrally administered nicotine augments antinociception resulting from μ-opioid receptor activation in murine models.[65,66] Nicotine administration also produces an up-regulation of μ-opioid receptors in the striatum of rats.[67] However, other studies reported that μ-opioid receptor antagonism only incompletely attenuates[61,68] or does not reduce nicotine-induced antinociception.[8,69,70]

The serotonergic system likely also plays an important role in modulating nicotine-induced antinociception.[71–74] The antinociceptive effects of nicotine are reduced in a dose-dependent manner by serotonergic $5HT_{1A}$ agonists such as 8-OH-DPAT (8-hydroxy- 2-(di-n-propylamino)tetraline) and buspirone.[71] Inhibition of serotonin biosynthesis and subsequent depletion of available serotonin stores (*e.g.*, using parachlorophenylalanine) enhances the antinociceptive effects of nicotine.[72] However, the exact mechanisms and pathways underlying serotonergic modulation of the antinociception induced by acute exposure to nicotine are not clear.

Chronic nicotine exposure results in tolerance to nicotine-induced antinociception.[57,61,75] In rats, continuous administration of nicotine produces antinociception for only a short period of time after initiation of administration.[58,68,76] Chronic exposure causes widespread adaptive changes in the endogenous opioid system which may affect processing of nociceptive stimuli in general.[67,75,77,78] Compared with nicotine-naïve rats, nicotine-tolerant rats develop greater mechanical hyperalgesia after spinal nerve ligation or sciatic nerve injury.[79,80] The increased mechanical hyperalgesia was associated with increased spinal dynorphin levels[81] as well as increased production of cytokines centrally and peripherally.[79] Thus, when evaluating the behavioral effects of chronic nicotine exposure a complex interplay among receptor desensitization, overexpression, and neural plasticity in associated nociceptive pathways must be considered. Furthermore, nicotine withdrawal was associated with hyperalgesia in nicotine-tolerant rodents,[57,82,83] which was reversible by morphine administration.[82]

Other Nicotine Acetylcholine Receptor Ligands. Nicotine may exert analgesic effects *via* one or many different nAChR subtypes. Multiple studies have been conducted in an attempt to obtain more selective analgesic compounds. These studies may also help to identify the mechanisms of analgesic action for nAChR ligands.

Agonists of $\alpha 4\beta 2$ Nicotine Acetylcholine Receptors. The demonstration that the alkaloid isolated from the skin of the Ecuadorian poisonous-arrow frog *Epipedobates tricolor* is a potent analgesic prompted considerable research into this and other nicotinic agonists as potentially clinically useful agents.[17] Epibatidine has a high affinity for and is a potent agonist of the $\alpha 4\beta 2$ and $\alpha 7$ nAChRs.[84,85] Epibatidine has potent analgesic effects in a variety of murine pain models, including the hot plate assay, tail-flick test, and carrageenan pain model.[16–18] The analgesic actions of epibatidine are blocked by the centrally acting nAChR antagonist mecamylamine, but not by the peripherally acting antagonist hexamethonium, or naloxone.[17,86,87] Importantly, the analgesic properties of epibatidine are not affected by blockade of α-bungarotoxin-sensitive receptors with methyllycaconitine, suggesting that $\alpha 7$ nicotinic receptors are not involved in analgesia.[15] The azetidine analog of epibatidine, ABT-594 [(*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine] has a similar affinity for the $\alpha 4\beta 2$ nAChRs, but a very low affinity for $\alpha 7$ nAChRs, ganglionic, and muscular nAChRs.[19] Accordingly, ABT-594 is a potent oral analgesic in a variety of pain models in rodents and maintains its analgesic effects with repeated dosing.[88–90] Like epibatidine, the analgesic actions of ABT-594 are blocked by mecamylamine, but not by hexamethonium or naltrexone.[91] Sazetidine-A, a partial agonist of the $\alpha 4\beta 2$ receptor, produces analgesia in a formalin test in rats.[20,92] Varenicline, an effective medication for smoking cessation, is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nAChRs,[93] and it has analgesic effects in the rat formalin test.[94]

Unfortunately, $\alpha 4\beta 2$ ligands have significant unacceptable side effects. Both epibatidine and ABT-594 show serious side effects at or near doses required for analgesia. Epibatidine produces hypertension, neuromuscular paralysis, seizures, and death in rodents.[17,95] Although ABT-594 showed reduced side effects compared with epibatidine in some animal studies,[88–90] it produces hypothermia, seizures, and hypertension in rats (like high-dose nicotine), and after repeated exposure rats develop an abstinence syndrome.[96] This side effect and toxicity profile has precluded investigation of these agents in human trials.[97] As a partial agonist, sazetidine-A administration may be less limited by undesirable effects,[20] but further preclinical studies are needed.

Investigation of the mechanism of action of $\alpha 4\beta 2$ agonists suggests that analgesia is mediated predominantly *via* a supraspinal effect. Epibatidine administration produces dopamine release from striatal slices, norepinephrine release from the hippocampus and thalamus, and excitatory amino acids from the spinal cord.[98,99] Epibatidine activates the nucleus raphe magnus, dorsal raphe, and locus coeruleus, all areas that are involved in the central modulation of pain *via* descending inhibitory pathways.[45,100,101] The analgesic properties of epibatidine are attenuated by phenoxybenzamine and *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4, a neurotoxin that depletes norepinephrine) but not by dopamine antagonists.[15,99]

Antagonists of α9 or α10 nAChRs. Highly selective α9 or α10 nAChR antagonists derived from cone snail toxins have been developed, including Vc1.1, RgIA, and PeIA.[102–104] The α-conotoxin Vc1.1 attenuates the increase in axonal excitability of human unmyelinated C-fiber axons produced by nicotine.[105] Subcutaneous and intramuscular administration of Vc1.1 produces analgesia in neuropathic pain models in rats that is sustained without signs of tolerance.[102,106] Interestingly, administration of Vc1.1 also improves nerve recovery from and attenuates the inflammatory response to nerve injury.[102,106] It has been postulated that antagonism of the α9 or α10 nAChRs produces analgesia in part by immunomodulation.[107] The exact role, if any, of other nAChR ligands is presently unclear.

Human Studies

Experimental Pain Studies. Nicotine produces analgesia in human models of experimental pain. In general, nicotine administration *via* nasal spray or transdermal patches reduces pain sensitivity in both smokers and nonsmokers.[10,108] Smoking a cigarette decreases awareness of and increases tolerance to some experimental pain stimuli,[10,12,13] but these effects may involve additional substances in cigarette smoke, as they are attenuated when nicotine-depleted cigarettes are smoked.[9,11]

Results from studies with humans are more difficult to interpret than are results from animal studies for several reasons. First, many human studies involve those habituated to cigarette smoke, because nicotine administration to naïve subjects may be associated with unpleasant side effects such as nausea. Beyond the effects of prolonged nicotine exposure on nAChRs, the timing of the experimental nicotine exposure in relation to the last cigarette smoked may be important given the rapid decrease in nicotine levels in the absence of continued smoking (half-life of ∼1 h).[109] Second, analgesic effects of nicotine may differ across experimental pain models (table 1). Although nicotine consistently increases pain thresholds in cold pressor tests,[9,11,13,110] results are inconsistent with heat[108,111,112] or electrical stimulation pain models.[10,12,113–115] Finally, the effects of nicotine may depend on sex. Studies of male subjects find that smoking consistently produces analgesia,[9,11,13,112] whereas studies with only or mostly females report negative results.[113,116] In one study involving both sexes, transdermal nicotine increased pain thresholds to electrical stimulation in males but not females.[10] However, two other studies found no sex differences in the effects of smoking on cold pressor pain.[13,110]

As with animal studies, the mechanisms of nicotine analgesia are not completely understood in humans, especially because the range of experimental options is more limited. Nicotine effects on pain responses may represent treatment of nicotine withdrawal rather than direct analgesic effects in studies examining smokers deprived of nicotine.[117] However, the antinociceptive effect of nicotine is present in both nicotine-deprived subjects and those who have maintained regular smoking.[9,11,108] Nicotine administration in cigarette smoke may also confound interpretation of analgesic effects. Smoking increases blood pressure and heart rate,[116] which can reduce pain sensitivity.[108,118,119] However, blockade of ß-adrenoreceptors to attenuate sympathetic activation caused by smoking does not affect heat pain sensation,[12] although it blunts antinociceptive effects of nicotine in heavy, but not light or moderate, smokers in an electrical stimulation experimental pain model[120] (see also discussion in the section "Potential Mechanisms of Chronic Pain in Cigarette Smokers").

Postoperative Pain. Several studies have explored the possibility that systemic nicotine could be used to provide postoperative analgesia. In a placebo-controlled trial of nonsmoking female patients undergoing uterine surgery *via* a low transverse incision, nicotine enhanced morphine analgesia.[121] Patients who received a single 3 mg dose of nicotine nasal spray before emergence from general anesthesia reported lower pain scores during the first hour after surgery, used half the amount of morphine, and reported less pain 24 h after surgery.[121] However, another study from this group found that the administration of 3 mg of intranasal nicotine did not reduce analgesic requirements in nonsmoking females undergoing open uterine surgery.[122] In the latter study, patients were assigned to a general anesthetic with either isoflurane or propofol and administered nicotine or placebo nasal spray. In both anesthetic groups, nicotine failed to significantly reduce postoperative opioid requirements, although the sample sizes in this study were small. In a study of both male and female nonsmokers, transdermal nicotine patches applied immediately before surgery and removed the night after surgery improved immediate and sustained (5 days) analgesia after abdominal and pelvic procedures, with a ceiling response above the 5 mg/24 h dose.[123] In males undergoing radical retropubic prostatectomy, nonsmokers who received a 7 mg/24 h transdermal nicotine patch applied before general anesthesia significantly reduced morphine requirements in the first 24 h postoperatively.[124] In contrast, Turan *et al.* reported that 21 mg/24 h transdermal nicotine patches did not improve postoperative pain or have opioid-sparing effects in females undergoing abdominal hysterectomy.[125] However, 61% of the subjects in this study were smokers and thus chronically exposed to nicotine. In another study, smokers undergoing abdominal or pelvic surgery did not report improved analgesia or reduced opioid consumption with preoperative application of transdermal nicotine in doses from 5 to 15 mg/24 h.[126] Thus, it appears that in most studies of humans who do not smoke, nicotine has antinociceptive effects in a clinical setting, but in smokers, receptor desensitization and/or withdrawal effects may limit any analgesic effects of perioperative nicotine administration. Larger confirmatory studies in both smokers and nonsmokers are needed to determine whether nicotine administration has the potential to be a useful adjunct analgesic. Studies are also needed to determine whether the side

Table 1. Effects of Smoking and Nicotine on Experimental Pain in Humans

			Subjects			Painful Stimulus		
				Smoker+ Nonsmoker				
Study	Year	Comparison	Smoking Status	Male (No.)	Female (No.)	Cold Pressor	Electrical	Thermal Heat
Positive studies								
Nesbitt[148]	1973	Within subjects (prepost smoking)	Unknown	30			T +	
Silverstein[149]	1982	Between subjects (abstinence group *vs.* high nicotine cigarettes group)	Deprived	38			Th +, T +	
Pomerleau[11]	1984	Within subject (zero nicotine cigarettes *vs.* usual cigarettes)	Minimally deprived	6		Th +, T +		
Fertig[9]	1986	Within subject (zero nicotine cigarettes *vs.* usual cigarettes)	Minimally deprived	10		Th +, T +		
Pauli[112]	1993	Within subjects (abstinence *vs.* smoking)	Deprived Minimally deprived	9				Th + Th 0
Perkins[108]	1994	Within subjects (prepost nicotine nasal spray)	Deprived	10 + 10				Th +*
		Within subjects (placebo *vs.* nicotine)	Deprived	6 + 6	6 + 6			Th +*†
		Within subjects (placebo *vs.* nicotine)	Deprived	9 + 9	9 + 9			Th +*†
Lane[111]	1995	Within subjects (abstinence *vs.* smoking)	Deprived	11	7			T +†
Jamner[10]	1998	Within subject (prepost nicotine patch)	Deprived	17 + 13	21 + 23		Th +, T + (male)*	
Kanarek[13]	2004	Within subjects (abstinence *vs.* smoking)	Deprived	24	25	Th +, T +		
Nastase[110]	2007	Within subjects (abstinence *vs.* smoking)	Deprived	12	11	Th +, T +		
Negative studies								
Waller[12]	1983	Between subjects (abstinence *vs.* smoking)	Deprived	33			Th 0, T 0	
Mueser[114]	1984	Within subjects (abstinence *vs.* smoking)	Minimally deprived	8	16		Th 0, T 0	
Shiffman[116]	1984	Within subjects (sham *vs.* smoking)	Unknown	2	8		Th 0, T 0	
Sult[151]	1986	Within subjects (sham *vs.*smoking)	Deprived		16	Th 0, T 0	Th 0, T 0	
Knott[113]	1990	Within subjects (abstinence *vs.* smoking)	Deprived		14		Subject rating 0	

"Deprived" smokers were abstinent from smoking for at least 3 h before the experiment. "Minimally deprived" smokers were abstinent for less than 3 h before the experiment.

* Also observed in nonsmokers. † Sex difference not studied.

+ = increased by smoking/nicotine; 0 = no change with smoking/nicotine; T = tolerance; Th = threshold.

effects of perioperative nicotine administration can be tolerated. Available studies indicate that intraoperative nicotine does not produce marked hemodynamic changes,[123] but it may be associated with increased postoperative nausea,[124] a well known effect in nicotine-naïve subjects.

Chronic Pain in Cigarette Smokers

Smoking as a Risk Factor for Chronic Painful Conditions

Several epidemiologic studies show an association between smoking and chronic painful conditions. Leboeuf-Yde *et al.* performed a systematic literature review on the association between smoking and low back pain based on 47 studies published between 1974 and 1996.[127] Many, but not all, studies find a positive association between smoking and low back pain, with the results from studies with larger samples being more likely to reach statistical significance. Goldberg *et al.* reviewed publications from 1976 through mid-1997 on the association between smoking and nonspecific back pain and also found that smoking is associated with nonspecific back pain in some, but not all, of the studies.[128] Both of these reviews indicated that the lack of consistency among studies regarding dose response, temporality, and reversibility of nicotine-induced analgesia is an important factor to be considered when making conclusions regarding causality. Moreover, potential confounding effects could not be ruled out based on available evidence because many of the studies were of poor methodological quality. Subsequent studies, published after these reviews, based on epidemiologic data collected from both general and occupational health populations across different geographic regions continue to demonstrate the positive association between smoking status and back pain as well as other painful conditions.[21–32] However, there are also several more recent studies that failed to find any association between smoking and chronic pain.[129–132] Consideration of the potential relationship between smoking status and painful conditions is further complicated by the fact that smoking can produce changes in central nervous function that persist long after subjects stop smoking.[133] Thus, there may be a difference in the susceptibility to chronic pain between never and former smokers, which is often not taken into account in clinical studies. Indeed, some studies suggest that an association of smoking history and chronic pain conditions also exists among former smokers.[31,33,134]

In addition to these epidemiologic studies, several additional recent prospective cohort studies provide further evidence for a relationship between smoking and chronic painful conditions. A prospective cohort study of adolescents in Finland demonstrated that daily smoking of more than 9 cigarettes at age 16 predicted pain symptoms (adjusted odds ratio [OR] 2.80; 95% CI 1.11–7.09, adjusted for other factors associated with pain) and was associated with persistent low back pain at age 18 among girls, with a clear dose-response relationship (adjusted OR 2.57; 95% CI 1.03–6.46).[27] Another longitudinal study in Finland followed a cohort of adolescents for an average of 11 yr and found that daily smoking was one of the strongest risk factors for low back pain hospitalization (adjusted hazard ratio 1.4; 95% CI 1.1–1.7).[26] The associations persisted into adulthood. In the same cohort, daily smoking was a risk factor for lumbar discectomy among males (adjusted hazard ratio 1.5; 95% CI 1.1–2.2).[135] In a British birth cohort, incident low back pain at age 32 to 33 yr was predicted by moderate or heavy smoking in early adulthood (adjusted OR 1.63, 95% CI 1.23–2.17).[32] In a study in young adults in Norway, smoking in 1990 was associated with moderate or severe pain in 1994 (adjusted OR 2.28; 95% CI 1.32–3.94).[22] In a longitudinal study following 9,600 twins for 8 yr, smoking at baseline showed a dose-response relationship with low back pain at follow-up (adjusted OR up to 4.0 for those smoking more than 20 cigarettes a day).[24] In a Finnish occupational cohort, smoking of long duration (more than 15 yr), increased the risk of incidental sciatic pain (adjusted OR 2.3; 95% CI 1.3, 3.9).[28] In a cohort of metal industry employees followed from 1973 to 2000, the adjusted hazard ratio of heavy smokers for hospitalization because of intervertebral disc disorders was 3.4 (95% CI 1.3–9.0) as compared with never-smokers.[25]

In addition to the studies showing an increased frequency of chronic painful conditions in cigarette smokers, others suggest that among those with chronic pain, smokers complain of greater pain intensity and an increased number of painful sites.[33,34] In patients presenting to pain rehabilitation, fibromyalgia treatment, and face pain clinics, those who smoke cigarettes report more pain and greater functional impairment, including scores measuring life interference and depression.[35–37,136] Smokers who have painful conditions are also more likely to have poorer outcomes. In a prospective cohort study of patients with arm pain, smoking status predicted the persistence of pain (OR 3.3, 95% CI 1.6–6.6).[137] In a 7-yr prospective cohort study of 34,754 employed men and women, current smoking was among the strongest predictors for future back pain disability (OR 1.4; 95% CI 1.2–1.7).[138] In a retrospective cohort of 15,268 active-duty personnel hospitalized for a common musculoskeletal condition between the years 1989–1996, heavy smoking (more than 1 pack/day) was associated with more disability due to knee conditions among males (hazard ratio 1.67; 95% CI 1.26–2.22).[139] In a study of Norwegian adults who had reported musculoskeletal pain, smoking was associated with more intense persistent pain (adjusted OR 1.58; 95% CI 1.24–2.00).[140] Other studies find that smokers with chronic low back pain experience greater long-term disability than nonsmokers.[141–144]

Potential Mechanisms of Chronic Pain in Smokers

Many factors may influence the relationship between smoking and chronic pain, as depicted in figure 2 and discussed in the following section. Several of these factors may interact to determine the ultimate impact of smoking on pain.

Altered Processing of Pain. As described above in the section on pharmacology of nAChRs, exposure to cigarette

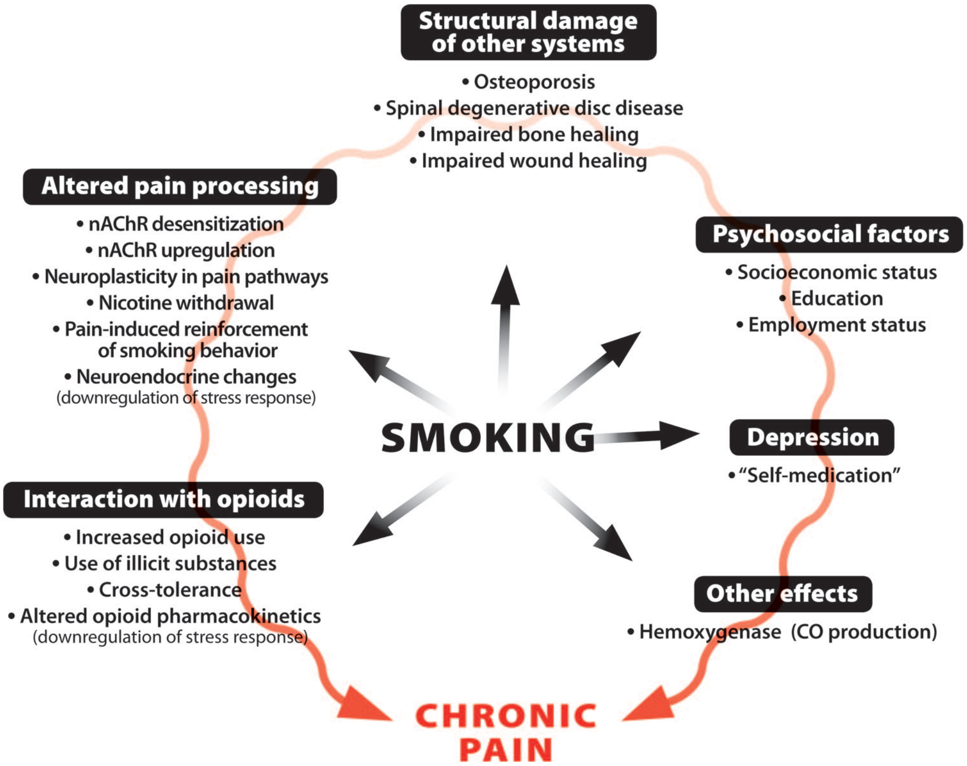

Fig. 2. Potential mechanisms of chronic pain in smokers. CO = carbon monoxide; nAChR = nicotine acetylcholine receptor.

smoke and nicotine produces analgesia in animal models, but receptor desensitization and tolerance develop quickly after continuous exposure and may persist for a considerable time.[57,58,61,64,75,145–147] In addition, withdrawal symptoms develop when nicotine intake is acutely eliminated or reduced and plasma nicotine levels fall below the relatively narrow range that smokers attempt to maintain during wakefulness. Withdrawal symptoms include both somatic complaints (*e.g.*, gastrointestinal symptoms and increased appetite) and affective symptoms (*e.g.*, craving for cigarettes, depressed mood, anxiety, dysphoria, and irritability).

Chronic exposure to cigarette smoke may change pain perception in smokers compared with nonsmokers (table 2). Compared with nonsmokers, smokers deprived of nicotine tend to have a shorter pain latency to heat pain and reduced tolerance to electrical pain stimulation.[148,149] However, the effects of smoking status may depend on both sex and the specific pain stimulus. For example, nicotine-deprived male smokers had higher threshold and tolerance to electrical pain stimulation compared with nonsmokers.[10] In a study involving both sexes where smokers were allowed to maintain their smoking behavior to minimize the influence of nicotine de-

Table 2. Comparison of Baseline Responses to Experimental Pain Stimuli between Smokers and Nonsmokers

		Subjects			Painful Stimulus			
			Smoker+Nonsmoker					
Study	Year	Smoking Status	Male	Female	Cold Pressor	Electrical	Thermal Heat	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.

privation and withdrawal, female smokers had greater threshold and tolerance to tourniquet-induced ischemic pain, whereas male smokers had increased threshold and tolerance to cold pressor pain.[118] In contrast, there were no significant differences between nonsmokers and smokers in their threshold or tolerance to heat pain, regardless of sex. The clinical significance of these stimuli-dependent differences in pain perception is not clear; indeed, when smoking status does affect perceptions in these experimental studies, it tends to blunt the perception of pain, which seems inconsistent with the increased frequency of painful disorders in smokers.

The interaction between pain and smoking might also reflect pain-induced reinforcement of smoking behaviors. A recent randomized experimental study reported that pain caused by cold pressor stimulation resulted in a shorter latency to smoke and that this process was fully mediated by self-reported pain-induced urge to smoke.[150] The effects of smoking on pain could reinforce smoking behavior by increasing the threshold for pain perception or serving as a coping strategy for the pain. In addition, nicotine withdrawal may enhance perception of pain. In animal models, nicotine withdrawal is associated with increased sensitivity to pain stimuli.[57,76,82,83] Thus, smokers may perceive a given stimulus as more painful (at least while deprived of cigarettes) and may smoke to relieve increased pain perceptions caused by incipient nicotine withdrawal when nicotine blood levels fall (*e.g.*, during sleep). Indeed, smoking a cigarette acutely increases the threshold and/or tolerance to thermal pain stimuli in smokers deprived of nicotine.[9,11,13,110–112] However, smoking does not consistently affect acute responses to electrical pain stimuli in deprived smokers.[12,113,114,116,148,149,151] It is not clear which (if any) of these stimuli are most clinically relevant to chronic pain states.

Smoking also causes changes in the neuroendocrine system that could modulate pain perception. In general, the stress response (sympathetic and hypothalamic-pituitary-adrenal activation) causes a decrease in pain perception. Although smoking a cigarette can acutely increase these measures, chronic activation by smoking actually can down-regulate these systems, with impaired baroreceptor function and decreases in β-endorphin levels.[118,152–155] The normal relationship between stress-induced increases in measures of hypothalamic-pituitary-adrenal activation and analgesia is absent in smokers, providing evidence for smoking-induced dysregulation in endogenous systems that regulate pain. Sex-specific neuroendocrine mechanisms may also contribute to the sex differences in the effect of smoking on pain; for example, estradiol concentrations are chronically reduced in women smokers whereas norepinephrine concentrations are increased only among male smokers.[118]

Structural Damage to Other Systems. In addition to the changes in pain processing, smoking can induce structural changes in other systems that will predispose patients to painful conditions. Smoking is a risk factor for osteoporosis, lumbar disc diseases, and impaired bone healing.[156–158] One of the possible underlying mechanisms is that cigarette smoking impairs oxygen delivery to tissues by increasing sympathetic outflow and carboxyhemoglobin levels.[159–162] Thus, smoking may accelerate degenerative processes which make the body more vulnerable to injury. Smoking also can interfere with wound healing, which could contribute to prolonged pain after trauma, surgery, or other injuries.[163]

Association with Depression. Symptoms of depression are more common in smokers as compared with nonsmokers.[164–167] It is possible that smoking may increase susceptibility to the development of depression. Many smokers report that smoking elevates their mood, so smoking may represent a “self-medication” of depression by cigarettes. Indeed, the frequency of smoking is very high in patients with a variety of psychiatric disorders,[168–170] and this explanation is frequently invoked to explain this association. It may also be possible that susceptibility to nicotine dependence and depression share a common etiology. In addition, depression is linked to painful symptoms. Depression and pain share biologic pathways, and both are influenced by common biologic and social factors.[171–174] Symptoms of depression are relatively common in patients with chronic pain, and antidepressants are a frequent component of pain therapy. Thus, there may be a complex relationship among smoking, chronic pain, and depression, but few data exist that are useful in exploring this potential relationship.

Psychosocial Factors. As the prevalence of smoking has declined, the demographic characteristics of those who smoke have changed. Recent social network analyses show that smokers form isolated “clusters” that are becoming increasingly marginalized from others in society.[175,176] Smoking is also associated with poorer socioeconomic status, lower educational attainments, higher rates of divorce, and higher rates of unemployment.[1] These demographic characteristics are also observed among smokers who seek care for their painful symptoms.[35–37,136,177] Lower socioeconomic status and other psychosocial stressors are also related to a higher prevalence of chronic pain and poorer outcomes.[178–181] All of these factors may impair the ability of individuals to cope with their pain symptoms and thus contribute to chronic painful states. However, such psychosocial factors do not entirely explain the increased severity of painful conditions in smokers, as recent studies show that the symptoms of smokers presenting to a pain clinic in a tertiary care center were more severe than those of nonsmokers, even after controlling for demographic factors.[36,37,136]

Opioid Use. A recent population-based study shows that current and former heavy smokers are more likely to use prescription analgesic drugs than never-smokers.[182] Among patients who were admitted to a pain rehabilitation program, smokers had a greater proportion of opioid use as well as a higher mean morphine equivalent dose compared to former smokers and never-smokers.[183] Further analysis suggested that male smokers consumed a greater quantity of opioids compared with female smokers.[184] Interaction between nAChRs and opioid receptor pathways may contribute to the use of opioid analgesics by smokers.

Opioid pathways may modulate both the analgesic effects of nicotine (as described in the section on animal studies) and the reinforcing properties of smoking that contribute to addiction. Indeed, cross-tolerance between nicotine and morphine is present in mice.[185] In humans, methadone use increases cigarette smoking,[186,187] whereas opioid antagonist naltrexone attenuates smoking behavior.[188,189] Mesolimbic dopaminergic pathways may be involved in this process because activation of both nAChRs and opioid receptors stimulates the release of dopamine in the nucleus accumbens in a synergistic fashion.[82,190,191] The nucleus accumbens mediates the rewarding effects of nicotine[192,193] and modulates pain perception.[194,195] Cigarette smoking is also associated with the abuse of alcohol and of illicit drugs, including heroin and cocaine, and there is a very high prevalence of smoking among those who abuse illicit opioids (more than 90%).[196] Thus, common behavioral or biologic factors may predispose individuals to nicotine dependence as well as dependence on other drugs, both licit and illicit. Indeed, substance use disorders may result from impaired decision-making ability in opioid-dependent smokers.[197]

Exposure to cigarette smoke may also alter the pharmacokinetics of opioids. A study in chronic pain patients showed that smokers reported higher pain scores and required more hydrocodone, but had lower serum hydrocodone levels, compared with nonsmokers.[198] Polycyclic aromatic hydrocarbons, a group of carcinogenic substances in cigarette smoke, substantially influence the activity of liver cytochrome P450 enzymes, primarily CYP1A2 and possibly CYP2E1.[199] In addition, UGT2B7, a subtype of uridine-diphosphate glucuronosyl transferase, is induced by polycyclic aromatic hydrocarbons.[200–202] Because morphine is primarily metabolized by these transferases, their induction may enhance morphine metabolism.[203,204] Furthermore, UDP-glucoronosyl transferase function may be modulated by CYP3A4.[205] However, how smoking status affects the metabolism of morphine and other opioid analgesics is still unclear.

Other Effects of Cigarette Smoking. Although most attention has been focused on the effects of nicotine on pain, any of the approximately 3,000 other constituents of cigarette smoke may also be involved in the development of painful conditions. For example, chronic exposure to carbon monoxide increases the level of heme oxygenase.[206,207] The heme oxygenase-carbon monoxide system influences a variety of cellular processes, including inflammation, oxidative stress, and apoptosis,[208] and heme oxygenase may participate in the development of neuropathic pain.[209] The possible involvement of the heme oxygenase-carbon monoxide system in the susceptibility of smokers to chronic pain needs further study.

In summary, current evidence supports the finding that smoking is a risk factor for chronic painful conditions, but several aspects of this relationship require further study. The complex relationship between the multiple factors associated with smoking (fig. 2) needs to be explored to elucidate the mechanisms responsible for this interaction. For example, more data are needed to determine whether smoking *per se* contributes to the development of pain, or whether it is a marker for other conditions such as depression or psychosocial factors that themselves are causal. To this end, studies need to carefully assess smoking history and to measure and control for the many other factors that may be associated with pain, including demographic factors, coexisting medical conditions, and medication use. Experimental human studies examining the effects of smoking and/or nicotine on pain need to carefully consider smoking history, including the extent of nicotine dependence as well as the withdrawal state of the subjects. The range of experimental pain models studied should be expanded, and their relevance to clinical painful conditions considered. The high prevalence of smoking and the large population affected by smoking related conditions or secondhand smoke make these studies urgently needed.

Clinical Implications

Management of Postoperative Pain in Cigarette Smokers

There are relatively few clinical studies of how smoking status affects acutely painful conditions in general and postoperative pain in particular. Several studies examined postoperative opioid consumption. After third molar extraction, those smoking more than 10 cigarettes a day used significantly more acetaminophen/codeine tablets compared with nonsmokers and light smokers, although the difference was modest (mean of 0.6 tablets).[210] A retrospective review of patients undergoing coronary artery bypass grafting demonstrated that smokers had a 33% greater opioid requirement in the first 48 h after surgery.[211] However, factors other than smoking status that are known to influence postoperative opioid use, such as age, sex, opioid tolerance, and surgical characteristics, were not controlled. In addition, female former and current smokers used more opioid analgesics than female never-smokers after gynecologic surgery.[212] All of these studies were observational, none attempted to analyze possible covariates that might influence opioid consumption, and none reported the level of analgesia achieved. In a general surgical population, smokers reported higher pain scores both before and after surgery but did not experience greater increases in pain postoperatively compared with nonsmokers,[213] although pain was only a secondary endpoint in this study and the study included a heterogeneous surgical population. Thus, based on the limited available evidence, increased postoperative analgesic requirements might be anticipated in cigarette smokers, although whether this effect (if present) is of sufficient magnitude to warrant a change in clinical approach (*e.g.*, a more aggressive use of regional analgesia) is not clear. Clearly more data are needed from carefully conducted prospective clinical studies.

As discussed above in the section on human studies–postoperative pain, some (but not all) studies find that systemic nicotine can contribute to postoperative analgesia in nonsmokers; whether nicotine replacement therapy could contribute to postoperative analgesia in smokers, both by preventing nicotine withdrawal and through the systemic effects of nicotine on pain perception, is unclear. However, in several placebo-controlled studies, nicotine patches did not improve postoperative analgesia in smokers,[125,126,214] nor did they affect nicotine withdrawal symptoms, which were minimal even in those smokers receiving placebo.[214] Thus, there is no evidence to suggest that routine perioperative nicotine replacement therapy in smokers will improve postoperative analgesia, although it may be efficacious in helping these patients maintain postoperative abstinence after hospital discharge,[205] which has several other benefits.

Outcomes of Chronic Pain Therapy in Smokers

The complex relationship between smoking, pain, and other comorbid conditions such as depression and substance use disorders may pose additional challenges to the treatment of smokers with painful symptoms. As discussed in the section on chronic pain, smokers presenting to pain treatment programs report more pain and greater functional impairment compared with nonsmokers.[35–37,136] Fishbain *et al.* found that current smokers were less likely to be employed compared with nonsmokers after multidisciplinary treatment for low back pain, implying more persistent disability.[215] Weingarten *et al.* observed that 50% of smokers presenting to an outpatient tertiary pain clinic were unemployed or disabled, compared with 18% of nonsmokers.[36] However, Hooten *et al.* reported that in an observational study of outcomes from a 3-week multidisciplinary pain rehabilitation program, despite the greater pain and functional impairment reported by smokers at program entry, their treatment responses were either not different or actually better than for nonsmokers.[35] Importantly, the 3-week treatment program also incorporated an aggressive attempt to taper opioid use in those patients who were opioid-dependent, and nearly all participants discontinued opioid use. Success in opioid tapering in this program did not depend on smoking status, regardless of sex.[35,184] Thus, it appears that smoking status does not prevent successful cognitive behavioral therapy and rehabilitation for pain treatment.

Smoking Cessation Interventions in Chronic Pain Patients

Smoking is the leading preventable cause of premature death in the United States.[216] A primary recommendation of the Clinical Practice Guideline for Treating Tobacco Use and Dependence is that whenever patients contact the health care system, a systematic effort should be made to identify tobacco users, strongly urge them to quit, and provide aid to do so.[217] Consideration of the potential role of clinician interventions to address smoking as a part of pain therapy raises several interesting issues.[218,219] Certainly, patients with chronic pain, like all other patients, would enjoy the dramatic benefits of smoking cessation on long-term health. However, there are also concerns. Given the complex relationship among pain, smoking, and comorbid conditions such as depression and substance use disorders, it is not clear how tobacco abstinence would affect pain symptoms, either in the short or longer term. In the short term, to the extent that systemic nicotine provides acute analgesia, abstinence might acutely worsen painful symptoms and remove a means that many smokers perceive as useful in controlling stress and anxiety. Nicotine withdrawal symptoms accompanying acute abstinence might also complicate concurrent efforts to treat pain. In the long term, recovery from the effects of long-term exposure to nicotine may improve chronic painful states, although this remains to be determined. Adoption of coping strategies other than smoking may also improve adaptive responses to persistent pain and improve functional status.

Although data are very limited, it appears that motivation and intent to quit smoking is similar in smokers with and without chronic pain.[220] However, observational studies suggest that very few smokers entering chronic pain treatment successfully quit, even when offered efficacious tobacco intervention services.[35,215] Thus, there is an urgent need for more research about how tobacco abstinence affects chronic pain and the development of effective methods to help smokers with chronic pain quit. There may be an instructive parallel with psychiatric disease. Psychiatric hospitals were among the last healthcare facilities to ban smoking because of the high prevalence of smoking among these patients and the assumption that abstinence would worsen mental health outcomes.[221,222] However, experience has shown this not to be the case, and now considerable efforts are under way specifically targeting tobacco interventions to these patients.[223–227] A similar approach may be warranted for the chronic pain patient. However, such approaches will require a sufficient evidence base regarding the acute and chronic effects of abstinence on painful conditions, and the development of practical, efficacious interventions that can be readily applied in the clinical setting.

References

1. Centers for Disease Control and Prevention (CDC): Cigarette smoking among adults–United States, 2007. MMWR Morb Mortal Wkly Rep 2008; 57:1221–6
2. Centers for Disease Control and Prevention (CDC): Disparities in secondhand smoke exposure–United States, 1988–1994 and 1999–2004. MMWR Morb Mortal Wkly Rep 2008; 57:744–7
3. Davis L, Pollock LJ, Stone TT: Visceral pain. Surg Gynecol Obstet 1932; 55:418–27
4. Aceto MD, Awaya H, Martin BR, May EL: Antinociceptive action of nicotine and its methiodide derivatives in mice and rats. Br J Pharmacol 1983; 79:869–76
5. Mansner R: Relation between some central effects of nicotine and its brain levels in the mouse. Ann Med Exp Biol Fenn 1972; 50:205–12
6. Phan DV, Dóda M, Bite A, György L: Antinociceptive activity of nicotine. Acta Physiol Acad Sci Hung 1973; 44:85–93
7. Sahley TL, Berntson GG: Antinociceptive effects of cen-

tral and systemic administrations of nicotine in the rat. Psychopharmacology (Berl) 1979; 65:279–83

8. Tripathi HL, Martin BR, Aceto MD: Nicotine-induced antinociception in rats and mice: Correlation with nicotine brain levels. J Pharmacol Exp Ther 1982; 221:91–6
9. Fertig JB, Pomerleau OF, Sanders B: Nicotine-produced antinociception in minimally deprived smokers and ex-smokers. Addict Behav 1986; 11:239–48
10. Jamner LD, Girdler SS, Shapiro D, Jarvik ME: Pain inhibition, nicotine, and gender. Exp Clin Psychopharmacol 1998; 6:96–106
11. Pomerleau OF, Turk DC, Fertig JB: The effects of cigarette smoking on pain and anxiety. Addict Behav 1984; 9:265–71
12. Waller D, Schalling D, Levander S, Edman G: Smoking, pain tolerance, and physiological activation. Psychopharmacology (Berl) 1983; 79:193–8
13. Kanarek RB, Carrington C: Sucrose consumption enhances the analgesic effects of cigarette smoking in male and female smokers. Psychopharmacology (Berl) 2004; 173:57–63
14. Marubio LM, del Mar Arroyo-Jimenez M, Cordero-Erausquin M, Léna C, Le Novère N, de Kerchove d'Exaerde A, Huchet M, Damaj MI, Changeux JP: Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. Nature 1999; 398:805–10
15. Rao TS, Correa LD, Reid RT, Lloyd GK: Evaluation of anti-nociceptive effects of neuronal nicotinic acetylcholine receptor (NAChR) ligands in the rat tail-flick assay. Neuropharmacology 1996; 35:393–405
16. Qian C, Li T, Shen TY, Libertine-Garahan L, Eckman J, Biftu T, Ip S: Epibatidine is a nicotinic analgesic. Eur J Pharmacol 1993; 250:R13–4
17. Spande TF, Garraffo HM, Edwards MW, Yeh HJC, Pannell L, Daly JW: Epibatidine: A novel (chloropyridyl)azabicycloheptane with potent analgesic activity from an Ecuadoran poison frog. J Am Chem Soc 1992; 114:3475–8
18. Rupniak NM, Patel S, Marwood R, Webb J, Traynor JR, Elliott J, Freedman SB, Fletcher SR, Hill RG: Antinociceptive and toxic effects of (+)-epibatidine oxalate attributable to nicotinic agonist activity. Br J Pharmacol 1994; 113:1487–93
19. Donnelly-Roberts DL, Puttfarcken PS, Kuntzweiler TA, Briggs CA, Anderson DJ, Campbell JE, Piattoni-Kaplan M, McKenna DG, Wasicak JT, Holladay MW, Williams M, Arneric SP: ABT-594 [(R)-5-(2-Azetidinylmethoxy)-2-Chloropyridine]: A novel, orally effective analgesic acting via neuronal nicotinic acetylcholine receptors: I. In vitro characterization. J Pharmacol Exp Ther 1998; 285:777–86
20. Cucchiaro G, Xiao Y, Gonzalez-Sulser A, Kellar KJ: Analgesic effects of Sazetidine-A, a new nicotinic cholinergic drug. ANESTHESIOLOGY 2008; 109:512–9
21. Andersson H, Ejlertsson G, Leden I: Widespread musculoskeletal chronic pain associated with smoking. An epidemiological study in a general rural population. Scand J Rehabil Med 1998; 30:185–91
22. Eriksen W, Natvig B, Rutle O, Bruusgaard D: Smoking and the functional status of young adults. Scand J Prim Health Care 1999; 17:174–9
23. Scott SC, Goldberg MS, Mayo NE, Stock SR, Poîtras B: The association between cigarette smoking and back pain in adults. Spine 1999; 24:1090–8
24. Hestbaek L, Leboeuf-Yde C, Kyvik KO: Are lifestyle-factors in adolescence predictors for adult low back pain? A cross-sectional and prospective study of young twins. BMC Musculoskelet Disord 2006; 7:27
25. Kaila-Kangas L, Leino-Arjas P, Riihimäki H, Luukkonen R, Kirjonen J: Smoking and overweight as predictors of hospitalization for back disorders. Spine 2003; 28:1860–8
26. Mattila VM, Saarni L, Parkkari J, Koivusilta L, Rimpelä A: Predictors of low back pain hospitalization—a prospective follow-up of 57,408 adolescents. Pain 2008; 139:209–17
27. Mikkonen P, Leino-Arjas P, Remes J, Zitting P, Taimela S, Karppinen J: Is smoking a risk factor for low back pain in adolescents? A prospective cohort study. Spine 2008; 33:527–32
28. Miranda H, Viikari-Juntura E, Martikainen R, Takala EP, Riihimäki H: Individual factors, occupational loading, and physical exercise as predictors of sciatic pain. Spine 2002; 27:1102–9
29. Miranda H, Viikari-Juntura E, Punnett L, Riihimäki H: Occupational loading, health behavior and sleep disturbance as predictors of low-back pain. Scand J Work Environ Health 2008; 34:411–9
30. Mustard CA, Kalcevich C, Frank JW, Boyle M: Childhood and early adult predictors of risk of incident back pain: Ontario Child Health Study 2001 follow-up. Am J Epidemiol 2005; 162:779–86
31. Palmer KT, Syddall H, Cooper C, Coggon D: Smoking and musculoskeletal disorders: Findings from a British national survey. Ann Rheum Dis 2003; 62:33–6
32. Power C, Frank J, Hertzman C, Schierhout G, Li L: Predictors of low back pain onset in a prospective British study. Am J Public Health 2001; 91:1671–8
33. John U, Hanke M, Meyer C, Völzke H, Baumeister SE, Alte D: Tobacco smoking in relation to pain in a national general population survey. Prev Med 2006; 43:477–81
34. Vogt MT, Hanscom B, Lauerman WC, Kang JD: Influence of smoking on the health status of spinal patients: The National Spine Network database. Spine 2002; 27:313–9
35. Hooten WM, Townsend CO, Bruce BK, Schmidt JE, Kerkvliet JL, Patten CA, Warner DO: Effects of smoking status on immediate treatment outcomes of multidisciplinary pain rehabilitation. Pain Med 2009; 10:347–55
36. Weingarten TN, Moeschler SM, Ptaszynski AE, Hooten WM, Beebe TJ, Warner DO: An assessment of the association between smoking status, pain intensity, and functional interference in patients with chronic pain. Pain Physician 2008; 11:643–53
37. Weingarten TN, Podduturu VR, Hooten WM, Thompson JM, Luedtke CA, Oh TH: Impact of tobacco use in patients presenting to a multidisciplinary outpatient treatment program for fibromyalgia. Clin J Pain 2009; 25:39–43
38. Taly A, Corringer PJ, Guedin D, Lestage P, Changeux JP: Nicotinic receptors: Allosteric transitions and therapeutic targets in the nervous system. Nat Rev Drug Discov 2009; 8:733–50
39. Unwin N: Refined structure of the nicotinic acetylcholine receptor at 4A resolution. J Mol Biol 2005; 346:967–89
40. Gotti C, Clementi F: Neuronal nicotinic receptors: From structure to pathology. Prog Neurobiol 2004; 74:363–96
41. Le Novère N, Corringer PJ, Changeux JP: The diversity of subunit composition in nAChRs: Evolutionary origins, physiologic and pharmacologic consequences. J Neurobiol 2002; 53:447–56
42. Couturier S, Bertrand D, Matter JM, Hernandez MC, Bertrand S, Millar N, Valera S, Barkas T, Ballivet M: A neuronal nicotinic acetylcholine receptor subunit (alpha 7) is developmentally regulated and forms a homo-oligomeric channel blocked by alpha-BTX. Neuron 1990; 5:847–56
43. Whiting PJ, Lindstrom JM: Purification and characterization of a nicotinic acetylcholine receptor from chick brain. Biochemistry 1986; 25:2082–93
44. Nashmi R, Lester HA: CNS localization of neuronal nicotinic receptors. J Mol Neurosci 2006; 30:181–4
45. Cucchiaro G, Chaijale N, Commons KG: The dorsal raphe nucleus as a site of action of the antinociceptive and

behavioral effects of the alpha4 nicotinic receptor agonist epibatidine. J Pharmacol Exp Ther 2005; 313:389–94

46. Rashid MH, Furue H, Yoshimura M, Ueda H: Tonic inhibitory role of alpha4beta2 subtype of nicotinic acetylcholine receptors on nociceptive transmission in the spinal cord in mice. Pain 2006; 125:125–35
47. Elgoyhen AB, Vetter DE, Katz E, Rothlin CV, Heinemann SF, Boulter J: alpha10: A determinant of nicotinic cholinergic receptor function in mammalian vestibular and cochlear mechanosensory hair cells. Proc Natl Acad Sci USA 2001; 98:3501–6
48. Lips KS, Pfeil U, Kummer W: Coexpression of [alpha]9 and [alpha]10 nicotinic acetylcholine receptors in rat dorsal root ganglion neurons. Neuroscience 2002; 115: 1–5
49. Peng H, Ferris RL, Matthews T, Hiel H, Lopez-Albaitero A, Lustig LR: Characterization of the human nicotinic acetylcholine receptor subunit alpha ([alpha]) 9 (CHRNA9) and alpha ([alpha]) 10 (CHRNA10) in lymphocytes. Life Sci 2004; 76:263–80
50. Pereira EF, Hilmas C, Santos MD, Alkondon M, Maelicke A, Albuquerque EX: Unconventional ligands and modulators of nicotinic receptors. J Neurobiol 2002; 53:479–500
51. Tassonyi E, Charpantier E, Muller D, Dumont L, Bertrand D: The role of nicotinic acetylcholine receptors in the mechanisms of anesthesia. Brain Res Bull 2002; 57:133–50
52. Benwell ME, Balfour DJ, Anderson JM: Evidence that tobacco smoking increases the density of (-)-[3H]nicotine binding sites in human brain. J Neurochem 1988; 50: 1243–7
53. Sallette J, Pons S, Devillers-Thiery A, Soudant M, Prado de Carvalho L, Changeux JP, Corringer PJ: Nicotine upregulates its own receptors through enhanced intracellular maturation. Neuron 2005; 46:595–607
54. Mukhin AG, Kimes AS, Chefer SI, Matochik JA, Contoreggi CS, Horti AG, Vaupel DB, Pavlova O, Stein EA: Greater nicotinic acetylcholine receptor density in smokers than in nonsmokers: A PET study with 2–18F-FA-85380. J Nucl Med 2008; 49:1628–35
55. Jinks SL, Carstens E: Activation of spinal wide dynamic range neurons by intracutaneous microinjection of nicotine. J Neurophysiol 1999; 82:3046–55
56. Schmelz M, Luz O, Averbeck B, Bickel A: Plasma extravasation and neuropeptide release in human skin as measured by intradermal microdialysis. Neurosci Lett 1997; 230:117–20
57. Anderson KL, Pinkerton KE, Uyeminami D, Simons CT, Carstens MI, Carstens E: Antinociception induced by chronic exposure of rats to cigarette smoke. Neurosci Lett 2004; 366:86–91
58. Carstens E, Anderson KA, Simons CT, Carstens MI, Jinks SL: Analgesia induced by chronic nicotine infusion in rats: Differences by gender and pain test. Psychopharmacology (Berl) 2001; 157:40–5
59. Caggiula AR, Epstein LH, Perkins KA, Saylor S: Different methods of assessing nicotine-induced antinociception may engage different neural mechanisms. Psychopharmacology (Berl) 1995; 122:301–6
60. Rowley TJ, Payappilly J, Lu J, Flood P: The antinociceptive response to nicotinic agonists in a mouse model of postoperative pain. Anesth Analg 2008; 107:1052–7
61. Simons CT, Cuellar JM, Moore JA, Pinkerton KE, Uyeminami D, Carstens MI, Carstens E: Nicotinic receptor involvement in antinociception induced by exposure to cigarette smoke. Neurosci Lett 2005; 389:71–6
62. Mogil JS, Wilson SG, Wan Y: Assessing nociception in murine subjects, Methods in Pain Research. Edited by Kruger L. Boca Raton, FL, CRC Press, 2001, pp 11–30
63. Berrendero F, Kieffer BL, Maldonado R: Attenuation of nicotine-induced antinociception, rewarding effects, and dependence in mu-opioid receptor knock-out mice. J Neurosci 2002; 22:10935–40
64. Berrendero F, Mendizábal V, Robledo P, Galeote L, Bilkei-Gorzo A, Zimmer A, Maldonado R: Nicotine-induced antinociception, rewarding effects, and physical dependence are decreased in mice lacking the preproenkephalin gene. J Neurosci 2005; 25:1103–12
65. Suh HW, Song DK, Choi SR, Chung KM, Kim YH: Nicotine enhances morphine- and beta-endorphin-induced antinociception at the supraspinal level in the mouse. Neuropeptides 1996; 30:479–84
66. Suh HW, Song DK, Lee KJ, Choi SR, Kim YH: Intrathecally injected nicotine enhances the antinociception induced by morphine but not beta-endorphin, D-Pen2,5-enkephalin and U50,488H administered intrathecally in the mouse. Neuropeptides 1996; 30:373–8
67. Wewers ME, Dhatt RK, Snively TA, Tejwani GA: The effect of chronic administration of nicotine on antinociception, opioid receptor binding and met-enkelphalin levels in rats. Brain Res 1999; 822:107–13
68. Campbell VC, Taylor RE, Tizabi Y: Effects of selective opioid receptor antagonists on alcohol-induced and nicotine-induced antinociception. Alcohol Clin Exp Res 2007; 31:1435–40
69. Christensen MK, Smith DF: Antinociceptive effects of the stereoisomers of nicotine given intrathecally in spinal rats. J Neural Transm Gen Sect 1990; 80:189–94
70. Khan IM, Buerkle H, Taylor P, Yaksh TL: Nociceptive and antinociceptive responses to intrathecally administered nicotinic agonists. Neuropharmacology 1998; 37:1515–25
71. Damaj MI, Glennon RA, Martin BR: Involvement of the serotonergic system in the hypoactive and antinociceptive effects of nicotine in mice. Brain Res Bull 1994; 33:199–203
72. Hunt TE, Wu WH, Zbuzek VK: The effects of serotonin biosynthesis inhibition on nicotine and nifedipine-induced analgesia in rats. Anesth Analg 1998; 87:1109–12
73. Iwamoto ET, Marion L: Adrenergic, serotonergic and cholinergic components of nicotinic antinociception in rats. J Pharmacol Exp Ther 1993; 265:777–89
74. Rogers DT, Iwamoto ET: Multiple spinal mediators in parenteral nicotine-induced antinociception. J Pharmacol Exp Ther 1993; 267:341–9
75. Galeote L, Kieffer BL, Maldonado R, Berrendero F: Mu-opioid receptors are involved in the tolerance to nicotine antinociception. J Neurochem 2006; 97:416–23
76. Yang CY, Wu WH, Zbuzek VK: Antinociceptive effect of chronic nicotine and nociceptive effect of its withdrawal measured by hot-plate and tail-flick in rats. Psychopharmacology (Berl) 1992; 106:417–20
77. Isola R, Zhang H, Duchemin AM, Tejwani GA, Neff NH, Hadjiconstantinou M: Met-enkephalin and preproenkephalin mRNA changes in the striatum of the nicotine abstinence mouse. Neurosci Lett 2002; 325:67–71
78. Walters CL, Cleck JN, Kuo YC, Blendy JA: Mu-opioid receptor and CREB activation are required for nicotine reward. Neuron 2005; 46:933–43
79. Brett K, Parker R, Wittenauer S, Hayashida K, Young T, Vincler M: Impact of chronic nicotine on sciatic nerve injury in the rat. J Neuroimmunol 2007; 186:37–44
80. Josiah DT, Vincler MA: Impact of chronic nicotine on the development and maintenance of neuropathic hypersensitivity in the rat. Psychopharmacology (Berl) 2006; 188: 152–61
81. Lough C, Young T, Parker R, Wittenauer S, Vincler M: Increased spinal dynorphin contributes to chronic nicotine-induced mechanical hypersensitivity in the rat. Neurosci Lett 2007; 422:54–8
82. Schmidt BL, Tambeli CH, Gear RW, Levine JD: Nicotine

withdrawal hyperalgesia and opioid-mediated analgesia depend on nicotine receptors in nucleus accumbens. Neuroscience 2001; 106:129–36

83. Biała G, Budzyńska B, Kruk M: Naloxone precipitates nicotine abstinence syndrome and attenuates nicotine-induced antinociception in mice. Pharmacol Rep 2005; 57:755–60
84. Gopalakrishnan M, Monteggia LM, Anderson DJ, Molinari EJ, Piattoni-Kaplan M, Donnelly-Roberts D, Arneric SP, Sullivan JP: Stable expression, pharmacologic properties and regulation of the human neuronal nicotinic acetylcholine alpha 4 beta 2 receptor. J Pharmacol Exp Ther 1996; 276:289–97
85. Sullivan JP, Donnelly-Roberts D, Briggs CA, Anderson DJ, Gopalakrishnan M, Piattoni-Kaplan M, Campbell JE, McKenna DG, Molinari E, Hettinger AM, Garvey DS, Wasicak JT, Holladay MW, Williams M, Arneric SP: A-85380 [3-(2(S)-azetidinylmethoxy) pyridine]: *In vitro* pharmacological properties of a novel, high affinity alpha 4 beta 2 nicotinic acetylcholine receptor ligand. Neuropharmacology 1996; 35:725–34
86. Damaj MI, Creasy KR, Grove AD, Rosecrans JA, Martin BR: Pharmacological effects of epibatidine optical enantiomers. Brain Res 1994; 664:34–40
87. Badio B, Daly JW: Epibatidine, a potent analgetic and nicotinic agonist. Mol Pharmacol 1994; 45:563–9
88. Bannon AW, Decker MW, Curzon P, Buckley MJ, Kim DJ, Radek RJ, Lynch JK, Wasicak JT, Lin NH, Arnold WH, Holladay MW, Williams M, Arneric SP: ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine]: A novel, orally effective antinociceptive agent acting *via* neuronal nicotinic acetylcholine receptors: II. In vivo characterization. J Pharmacol Exp Ther 1998; 285:787–94
89. Holladay MW, Wasicak JT, Lin NH, He Y, Ryther KB, Bannon AW, Buckley MJ, Kim DJ, Decker MW, Anderson DJ, Campbell JE, Kuntzweiler TA, Donnelly-Roberts DL, Piattoni-Kaplan M, Briggs CA, Williams M, Arneric SP: Identification and initial structure-activity relationships of (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594), a potent, orally active, non-opiate analgesic agent acting *via* neuronal nicotinic acetylcholine receptors. J Med Chem 1998; 41:407–12
90. Kesingland AC, Gentry CT, Panesar MS, Bowes MA, Vernier JM, Cube R, Walker K, Urban L: Analgesic profile of the nicotinic acetylcholine receptor agonists, (+)-epibatidine and ABT-594 in models of persistent inflammatory and neuropathic pain. Pain 2000; 86:113–8
91. Decker MW, Bannon AW, Buckley MJ, Kim DJ, Holladay MW, Ryther KB, Lin NH, Wasicak JT, Williams M, Arneric SP: Antinociceptive effects of the novel neuronal nicotinic acetylcholine receptor agonist, ABT-594, in mice. Eur J Pharmacol 1998; 346:23–33
92. Xiao Y, Fan H, Musachio JL, Wei ZL, Chellappan SK, Kozikowski AP, Kellar KJ: Sazetidine-A, a novel ligand that desensitizes alpha4beta2 nicotinic acetylcholine receptors without activating them. Mol Pharmacol 2006; 70:1454–60
93. Mihalak KB, Carroll FI, Luetje CW: Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol 2006; 70:801–5
94. Gao B, Hierl M, Clarkin K, Juan T, Nguyen H, Valk MV, Deng H, Guo W, Lehto SG, Matson D, McDermott JS, Knop J, Gaida K, Cao L, Waldon D, Albrecht BK, Boezio AA, Copeland KW, Harmange JC, Springer SK, Malmberg AB, McDonough SI: Pharmacological effects of nonselective and subtype-selective nicotinic acetylcholine receptor agonists in animal models of persistent pain. Pain 149:33–49
95. Bonhaus DW, Bley KR, Broka CA, Fontana DJ, Leung E, Lewis R, Shieh A, Wong EH: Characterization of the electrophysiological, biochemical and behavioral actions of epibatidine. J Pharmacol Exp Ther 1995; 272:1199–203
96. Boyce S, Webb JK, Shepheard SL, Russell MG, Hill RG, Rupniak NM: Analgesic and toxic effects of ABT-594 resemble epibatidine and nicotine in rats. Pain 2000; 85:443–50
97. Arneric SP, Holladay M, Williams M: Neuronal nicotinic receptors: A perspective on two decades of drug discovery research. Biochem Pharmacol 2007; 74:1092–101
98. Khan IM, Yaksh TL, Taylor P: Epibatidine binding sites and activity in the spinal cord. Brain Res 1997; 753:269–82
99. Sacaan AI, Menzaghi F, Dunlop JL, Correa LD, Whelan KT, Lloyd GK: Epibatidine: A nicotinic acetylcholine receptor agonist releases monoaminergic neurotransmitters: in vitro and in vivo evidence in rats. J Pharmacol Exp Ther 1996; 276:509–15
100. Cucchiaro G, Chaijale N, Commons KG: The locus coeruleus nucleus as a site of action of the antinociceptive and behavioral effects of the nicotinic receptor agonist, epibatidine. Neuropharmacology 2006; 50:769–76
101. Curzon P, Nikkel AL, Bannon AW, Arneric SP, Decker MW: Differences between the antinociceptive effects of the cholinergic channel activators A-85380 and (+/-)-epibatidine in rats. J Pharmacol Exp Ther 1998; 287:847–53
102. Vincler M, Wittenauer S, Parker R, Ellison M, Olivera BM, McIntosh JM: Molecular mechanism for analgesia involving specific antagonism of alpha9alpha10 nicotinic acetylcholine receptors. Proc Natl Acad Sci U S A 2006; 103:17880–4
103. Ellison M, Haberlandt C, Gomez-Casati ME, Watkins M, Elgoyhen AB, McIntosh JM, Olivera BM: Alpha-RgIA: A novel conotoxin that specifically and potently blocks the alpha9alpha10 nAChR. Biochemistry 2006; 45:1511–7
104. McIntosh JM, Plazas PV, Watkins M, Gomez-Casati ME, Olivera BM, Elgoyhen AB: A novel alpha-conotoxin, PeIA, cloned from Conus pergrandis, discriminates between rat alpha9alpha10 and alpha7 nicotinic cholinergic receptors. J Biol Chem 2005; 280:30107–12
105. Lang PM, Burgstahler R, Haberberger RV, Sippel W, Grafe P: A conus peptide blocks nicotinic receptors of unmyelinated axons in human nerves. Neuroreport 2005; 16:479–83
106. Satkunanathan N, Livett B, Gayler K, Sandall D, Down J, Khalil Z: Alpha-conotoxin Vc1.1 alleviates neuropathic pain and accelerates functional recovery of injured neurones. Brain Res 2005; 1059:149–58
107. Vincler M, McIntosh JM: Targeting the alpha 9alpha10nicotinic acetylcholine receptor to treat severe pain. Expert Opin Ther Targets 2007;11:891–7
108. Perkins KA, Grobe JE, Stiller RL, Scierka A, Goettler J, Reynolds W, Jennings JR: Effects of nicotine on thermal pain detection in humans. Exp Clin Psychopharmacol 1994; 2:95–106
109. Zevin S, Gourlay SG, Benowitz NL: Clinical pharmacology of nicotine. Clin Dermatol 1998; 16:557–64
110. Nastase A, Ioan S, Braga RI, Zagrean L, Moldovan M: Coffee drinking enhances the analgesic effect of cigarette smoking. Neuroreport 2007; 18:921–4
111. Lane JD, Lefebvre JC, Rose JE, Keefe FJ: Effects of cigarette smoking on perception of thermal pain. Exp Clin Psychopharmacol 1995; 3:140–7
112. Pauli P, Rau H, Zhuang P, Brody S, Birbaumer N: Effects of smoking on thermal pain threshold in deprived and minimally-deprived habitual smokers. Psychopharmacology (Berl) 1993; 111:472–6
113. Knott VJ: Effects of cigarette smoking on subjective and brain evoked responses to electrical pain stimulation. Pharmacol Biochem Behav 1990; 35:341–6

114. Mueser K, Waller D, Levander S, Schalling D: Smoking and pain–a method of limits and sensory decision theory analysis. Scand J Psychol 1984; 25:289–96
115. Shiffman S: Assessing smoking patterns and motives. J Consult Clin Psychol 1993; 61:732–42
116. Shiffman S, Jarvik ME: Cigarette smoking, physiological arousal, and emotional response: Nesbitt's paradox reexamined. Addict Behav 1984; 9:95–8
117. Schachter S: Pharmacological and psychological determinants of smoking. A New York University honors program lecture. Ann Intern Med 1978; 88:104–14
118. Girdler SS, Maixner W, Naftel HA, Stewart PW, Moretz RL, Light KC: Cigarette smoking, stress-induced analgesia and pain perception in men and women. Pain 2005; 114:372–85
119. Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CH: Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception. Proc Natl Acad Sci USA 1994; 91:6329–33
120. Rau H, Schweizer R, Zhuang P, Pauli P, Brody S, Larbig W, Heinle H, Muller M, Elbert T, Dworkin B, Birbaumer N: Cigarette smoking, blood lipids, and baroreceptor-modulated nociception. Psychopharmacology (Berl) 1993; 110:337–41
121. Flood P, Daniel D: Intranasal nicotine for postoperative pain treatment. ANESTHESIOLOGY 2004; 101:1417–21
122. Cheng SS, Yeh J, Flood P: Anesthesia matters: Patients anesthetized with propofol have less postoperative pain than those anesthetized with isoflurane. Anesth Analg 2008; 106:264–9
123. Hong D, Conell-Price J, Cheng S, Flood P: Transdermal nicotine patch for postoperative pain management: A pilot dose-ranging study. Anesth Analg 2008; 107:1005–10
124. Habib AS, White WD, El Gasim MA, Saleh G, Polascik TJ, Moul JW, Gan TJ: Transdermal nicotine for analgesia after radical retropubic prostatectomy. Anesth Analg 2008; 107:999–1004
125. Turan A, White PF, Koyuncu O, Karamanliodlu B, Kaya G, Apfel CC: Transdermal nicotine patch failed to improve postoperative pain management. Anesth Analg 2008; 107:1011–7
126. Olson LC, Hong D, Conell-Price JS, Cheng S, Flood P: A transdermal nicotine patch is not effective for postoperative pain management in smokers: A pilot dose-ranging study. Anesth Analg 2009; 109:1987–91
127. Leboeuf-Yde C: Smoking and low back pain. A systematic literature review of 41 journal articles reporting 47 epidemiologic studies. Spine 1999; 24:1463–70
128. Goldberg MS, Scott SC, Mayo NE: A review of the association between cigarette smoking and the development of nonspecific back pain and related outcomes. Spine 2000; 25:995–1014
129. Altinel L, Köse KC, Ergan V, Işik C, Aksoy Y, Ozdemir A, Toprak D, Doğan N: The prevalence of low back pain and risk factors among adult population in Afyon region, Turkey. Acta Orthop Traumatol Turc 2008; 42:328–33
130. Ghaffari M, Alipour A, Jensen I, Farshad AA, Vingard E: Low back pain among Iranian industrial workers. Occup Med (Lond) 2006; 56:455–60
131. Kovacs FM, Gestoso M, Gil del Real MT, López J, Mufraggi N, Méndez JI: Risk factors for non-specific low back pain in schoolchildren and their parents: A population based study. Pain 2003; 103:259–68
132. Mortimer M, Wiktorin C, Pernol G, Svensson H, Vingård E, MUSIC-Norrtälje study group. Musculoskeletal Intervention Center: Sports activities, body weight and smoking in relation to low-back pain: A population-based case-referent study. Scand J Med Sci Sports 2001; 11:178–84
133. Perkins KA, Gerlach D, Broge M, Sanders M, Grobe J, Fonte C, Cherry C, Wilson A, Jacob R: Quitting cigarette smoking produces minimal loss of chronic tolerance to nicotine. Psychopharmacology 2001; 158:7–17
134. Jakobsson U: Tobacco use in relation to chronic pain: Results from a Swedish population survey. Pain Med 2008; 9:1091–7
135. Mattila VM, Saarni L, Parkkari J, Koivusilta L, Rimpelä A: Early risk factors for lumbar discectomy: An 11-year follow-up of 57,408 adolescents. Eur Spine J 2008; 17: 1317–23
136. Weingarten TN, Iverson BC, Shi Y, Schroeder DR, Warner DO, Reid KI: Impact of tobacco use on the symptoms of painful temporomandibular joint disorders. Pain 2009; 147:67–71
137. Ryall C, Coggon D, Peveler R, Poole J, Palmer KT: A prospective cohort study of arm pain in primary care and physiotherapy–prognostic determinants. Rheumatology (Oxford) 2007; 46:508–15
138. Hagen KB, Tambs K, Bjerkedal T: A prospective cohort study of risk factors for disability retirement because of back pain in the general working population. Spine 2002; 27:1790–6
139. Lincoln AE, Smith GS, Amoroso PJ, Bell NS: The natural history and risk factors of musculoskeletal conditions resulting in disability among US Army personnel. Work 2002; 18:99–113
140. Eriksen WB, Brage S, Bruusgaard D: Does smoking aggravate musculoskeletal pain? Scand J Rheumatol 1997; 26: 49–54
141. Lanier DC, Stockton P: Clinical predictors of outcome of acute episodes of low back pain. J Fam Pract 1988; 27:483–9
142. Krousel-Wood MA, McCune TW, Abdoh A, Re RN: Predicting work status for patients in an occupational medicine setting who report back pain. Arch Fam Med 1994; 3:349–55
143. Oleske DM, Neelakantan J, Andersson GB, Hinrichs BG, Lavender SA, Morrissey MJ, Zold-Kilbourn P, Taylor E: Factors affecting recovery from work-related, low back disorders in autoworkers. Arch Phys Med Rehabil 2004; 85:1362–4
144. Oleske DM, Andersson GB, Lavender SA, Hahn JJ: Association between recovery outcomes for work-related low back disorders and personal, family, and work factors. Spine 2000; 25:1259–65
145. Damaj MI: Calcium-acting drugs modulate expression and development of chronic tolerance to nicotine-induced antinociception in mice. J Pharmacol Exp Ther 2005; 315:959–64
146. Wewers ME, Dhatt R, Tejwani GA: Naltrexone administration affects *ad libitum* smoking behavior. Psychopharmacology (Berl) 1998; 140:185–90
147. Wise EA, Price DD, Myers CD, Heft MW, Robinson ME: Gender role expectations of pain: Relationship to experimental pain perception. Pain 2002; 96:335–42
148. Nesbitt PD: Smoking, physiological arousal, and emotional response. J Pers Soc Psychol 1973; 25:137–44
149. Silverstein B: Cigarette smoking, nicotine addiction, and relaxation. J Pers Soc Psychol 1982; 42:946–50
150. Ditre JW, Brandon TH: Pain as a motivator of smoking: Effects of pain induction on smoking urge and behavior. J Abnorm Psychol 2008; 117:467–72
151. Sult SC, Moss RA: The effects of cigarette smoking on the perception of electrical stimulation and cold pressor pain. Addict Behav 1986; 11:447–51
152. Arosio E, De Marchi S, Rigoni A, Prior M, Lechi A: Effects of smoking on cardiopulmonary baroreceptor activation and peripheral vascular resistance. Eur J Clin Invest 2006; 36:320–5
153. Mancia G, Bertinieri G: Influence of smoking on barore-

ceptor function: 24 h measurements. J Hypertens 1999; 17:1507–8

154. Gerhardt U, Hans U, Hohage H: Influence of smoking on baroreceptor function: 24 h measurements. J Hypertens 1999; 17:941–6
155. Mancia G, Groppelli A, Di Rienzo M, Castiglioni P, Parati G: Smoking impairs baroreflex sensitivity in humans. Am J Physiol 1997; 273:H1555–60
156. An HS, Silveri CP, Simpson JM, File P, Simmons C, Simeone FA, Balderston RA: Comparison of smoking habits between patients with surgically confirmed herniated lumbar and cervical disc disease and controls. J Spinal Disord 1994; 7:369–73
157. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR: The effect of cigarette smoking and smoking cessation on spinal fusion. Spine 2000; 25:2608–15
158. Law MR, Hackshaw AK: A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: Recognition of a major effect. BMJ 1997; 315:841–6
159. Evans WF, Stewart HJ: Effect of smoking cigarets on the peripheral blood flow. Am Heart J 1943; 26:79–91
160. Jensen JA, Goodson WH, Hopf HW, Hunt TK: Cigarette smoking decreases tissue oxygen. Arch Surg 1991; 126: 1131–4
161. Monfrecola G, Riccio G, Savarese C, Posteraro G, Procaccini EM: The acute effect of smoking on cutaneous microcirculation blood flow in habitual smokers and nonsmokers. Dermatology 1998; 197:115–8

162 Richardson D: Effects of tobacco smoke inhalation on capillary blood flow in human skin. Arch Environ Health 1987; 42:19–25

163. Warner DO: Perioperative abstinence from cigarettes: Physiologic and clinical consequences. ANESTHESIOLOGY 2006; 104:356–67
164. Breslau N, Kilbey MM, Andreski P: Nicotine dependence and major depression. New evidence from a prospective investigation. Arch Gen Psychiatry 1993; 50:31–5
165. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P: Major depression and stages of smoking. A longitudinal investigation. Arch Gen Psychiatry 1998; 55: 161–6
166. Brown C, Madden PA, Palenchar DR, Cooper-Patrick L: The association between depressive symptoms and cigarette smoking in an urban primary care sample. Int J Psychiatry Med 2000; 30:5–26
167. Murphy JM, Horton NJ, Monson RR, Laird NM, Sobol AM, Leighton AH: Cigarette smoking in relation to depression: Historical trends from the Stirling County Study. Am J Psychiatry 2003; 160:1663–9
168. Breslau N: Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet 1995; 25:95–101
169. Dierker L, Donny E: The role of psychiatric disorders in the relationship between cigarette smoking and DSM-IV nicotine dependence among young adults. Nicotine Tob Res 2008; 10:439–46
170. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA: Nicotine dependence and psychiatric disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 2004; 61:1107–15
171. Bair MJ, Robinson RL, Katon W, Kroenke K: Depression and pain comorbidity: A literature review. Arch Intern Med 2003; 163:2433–45
172. Garcia-Cebrian A, Gandhi P, Demyttenaere K, Peveler R: The association of depression and painful physical symptoms–a review of the European literature. Eur Psychiatry 2006; 21:379–88
173. Gureje O: Psychiatric aspects of pain. Curr Opin Psychiatry 2007; 20:2–6
174. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R: Chronic spinal pain and physical-mental comorbidity in the United States: Results from the national comorbidity survey replication. Pain 2005; 113:331–9
175. Christakis NA, Fowler JH: The collective dynamics of smoking in a large social network. N Engl J Med 2008; 358:2249–58
176. Schroeder S: Stranded in the periphery—the increasing marginalization of smokers. N Engl J Med 2008; 358: 2284–6
177. Fishbain DA, Lewis JE, Cole B, Cutler RB, Rosomoff HL, Rosomoff RS: Variables associated with current smoking status in chronic pain patients. Pain Med 2007; 8:301–11
178. Fuentes M, Hart-Johnson T, Green CR: The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults. J Natl Med Assoc 2007; 99:1160–9
179. Hagen K, Vatten L, Stovner LJ, Zwart JA, Krokstad S, Bovim G: Low socio-economic status is associated with increased risk of frequent headache: A prospective study of 22718 adults in Norway. Cephalalgia 2002; 22:672–9
180. Feuerstein M, Sult S, Houle M: Environmental stressors and chronic low back pain: Life events, family and work environment. Pain 1985; 22:295–307
181. Klapow JC, Slater MA, Patterson TL, Atkinson JH, Weickgenant AL, Grant I, Garfin SR: Psychosocial factors discriminate multidimensional clinical groups of chronic low back pain patients. Pain 1995; 62:349–55
182. John U, Alte D, Hanke M, Meyer C, Völzke H, Schumann A: Tobacco smoking in relation to analgesic drug use in a national adult population sample. Drug Alcohol Depend 2006; 85:49–55
183. Hooten WM, Townsend CO, Bruce BK, Warner DO: The effects of smoking status on opioid tapering among patients with chronic pain. Anesth Analg 2009; 108:308–15
184. Hooten WM, Townsend CO, Bruce BK, Shi Y, Warner DO: Sex differences in characteristics of smokers with chronic pain undergoing multidisciplinary pain rehabilitation. Pain Med 2009; 10:1416–25
185. Zarrindast MR, Khoshayand MR, Shafaghi B: The development of cross-tolerance between morphine and nicotine in mice. Eur Neuropsychopharmacol 1999; 9:227–33
186. Chait LD, Griffiths RR: Effects of methadone on human cigarette smoking and subjective ratings. J Pharmacol Exp Ther 1984; 229:636–40
187. Schmitz JM, Grabowski J, Rhoades H: The effects of high and low doses of methadone on cigarette smoking. Drug Alcohol Depend 1994; 34:237–42
188. Epstein AM, King AC: Naltrexone attenuates acute cigarette smoking behavior. Pharmacol Biochem Behav 2004; 77:29–37
189. Rukstalis M, Jepson C, Strasser A, Lynch KG, Perkins K, Patterson F, Lerman C: Naltrexone reduces the relative reinforcing value of nicotine in a cigarette smoking choice paradigm. Psychopharmacology (Berl) 2005; 180: 41–8
190. Johnson SW, North RA: Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992; 12:483–8
191. Marshall DL, Redfern PH, Wonnacott S: Presynaptic nicotinic modulation of dopamine release in the three ascending pathways studied by *in vivo* microdialysis: Comparison of naive and chronic nicotine-treated rats. J Neurochem 1997; 68:1511–9
192. Clarke PB: Mesolimbic dopamine activation—the key to nicotine reinforcement? Ciba Found Symp 1990; 152: 153–62
193. Corrigall WA, Franklin KB, Coen KM, Clarke PB: The mesolimbic dopaminergic system is implicated in the

reinforcing effects of nicotine. Psychopharmacology (Berl) 1992; 107:285–9

194. Altier N, Stewart J: The role of dopamine in the nucleus accumbens in analgesia. Life Sci 1999; 65:2269–87
195. Gear RW, Aley KO, Levine JD: Pain-induced analgesia mediated by mesolimbic reward circuits. J Neurosci 1999; 19:7175–81
196. Hall SM: Nicotine interventions with comorbid populations. Am J Prev Med 2007; 33:S406–13
197. Rotheram-Fuller E, Shoptaw S, Berman SM, London ED: Impaired performance in a test of decision-making by opiate-dependent tobacco smokers. Drug Alcohol Depend 2004; 73:79–86
198. Ackerman WE 3rd, Ahmad M: Effect of cigarette smoking on serum hydrocodone levels in chronic pain patients. J Ark Med Soc 2007; 104:19–21
199. Zevin S, Benowitz NL: Drug interactions with tobacco smoking. An update. Clin Pharmacokinet 1999; 36:425–38
200. Bock KW, Gschaidmeier H, Heel H, Lehmköster T, Münzel PA, Raschko F, Bock-Hennig B: AH receptor-controlled transcriptional regulation and function of rat and human UDP-glucuronosyltransferase isoforms. Adv Enzyme Regul 1998; 38:207–22
201. Bock KW, Gschaidmeier H, Heel H, Lehmköster T, Münzel PA, Bock-Hennig BS: Functions and transcriptional regulation of PAH-inducible human UDP-glucuronosyltransferases. Drug Metab Rev 1999; 31:411–22
202. Mackenzie PI, Bock KW, Burchell B, Guillemette C, Ikushiro S, Iyanagi T, Miners JO, Owens IS, Nebert DW: Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. Pharmacogenet Genomics 2005; 15:677–85
203. Coffman BL, Rios GR, King CD, Tephly TR: Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos 1997; 25:1–4
204. Armstrong SC, Cozza KL: Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: Theory and clinical reality, part I. Psychosomatics 2003; 44:167–71
205. Takeda S, Ishii Y, Iwanaga M, Mackenzie PI, Nagata K, Yamazoe Y, Oguri K, Yamada H: Modulation of UDP-glucuronosyltransferase function by cytochrome P450: Evidence for the alteration of UGT2B7-catalyzed glucuronidation of morphine by CYP3A4. Mol Pharmacol 2005; 67:665–72
206. Carraway MS, Ghio AJ, Suliman HB, Carter JD, Whorton AR, Piantadosi CA: Carbon monoxide promotes hypoxic pulmonary vascular remodeling. Am J Physiol Lung Cell Mol Physiol 2002; 282:L693–702
207. Mirza A, Eder V, Rochefort GY, Hyvelin JM, Machet MC, Fauchier L, Bonnet P: CO inhalation at dose corresponding to tobacco smoke worsens cardiac remodeling after experimental myocardial infarction in rats. Toxicol Sci 2005; 85:976–82
208. Slebos DJ, Ryter SW, Choi AM: Heme oxygenase-1 and carbon monoxide in pulmonary medicine. Respir Res 2003; 4:7
209. Li X, Clark JD: Heme oxygenase type 2 participates in the development of chronic inflammatory and neuropathic pain. J Pain 2003; 4:101–7
210. Berge TI: Pattern of self-administered paracetamol and codeine analgesic consumption after mandibular third-molar surgery. Acta Odontol Scand 1997; 55:270–6
211. Creekmore FM, Lugo RA, Weiland KJ: Postoperative opiate analgesia requirements of smokers and nonsmokers. Ann Pharmacother 2004; 38:949–53
212. Woodside JR Jr: Female smokers have increased postoperative narcotic requirements. J Addict Dis 2000; 19:1–10
213. Warner DO, Patten CA, Ames SC, Offord K, Schroeder D: Smoking behavior and perceived stress in cigarette smokers undergoing elective surgery. ANESTHESIOLOGY 2004; 100:1125–37
214. Warner DO, Patten CA, Ames SC, Offord KP, Schroeder DR: Effect of nicotine replacement therapy on stress and smoking behavior in surgical patients. ANESTHESIOLOGY 2005; 102:1138–46
215. Fishbain DA, Lewis JE, Cutler R, Cole B, Steele Rosomoff R, Rosomoff HL: Does smoking status affect multidisciplinary pain facility treatment outcome? Pain Med 2008; 9:1081–90
216. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. JAMA 2004; 291:1238–45
217. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff: A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 2008; 35:158–76
218. Warner DO, American Society of Anesthesiologists Smoking Cessation Initiative Task Force: Feasibility of tobacco interventions in anesthesiology practices: A pilot study. ANESTHESIOLOGY 2009; 110:1223–8
219. Shi Y, Warner DO: Surgery as a teachable moment for smoking cessation. ANESTHESIOLOGY 2010; 112:102–7
220. Hahn EJ, Rayens MK, Kirsh KL, Passik SD: Brief report: Pain and readiness to quit smoking cigarettes. Nicotine Tob Res 2006; 8:473–80
221. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, Breslau N, Brown RA, George TP, Williams J, Calhoun PS, Riley WT: Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res 2008; 10:1691–715
222. Campion J, McNeill A, Checinski K: Exempting mental health units from smoke-free laws. BMJ 2006; 333:407–8
223. Shmueli D, Fletcher L, Hall SE, Hall SM, Prochaska JJ: Changes in psychiatric patients' thoughts about quitting smoking during a smoke-free hospitalization. Nicotine Tob Res 2008; 10:875–81
224. Harris GT, Parle D, Gagné J: Effects of a tobacco ban on long-term psychiatric patients. J Behav Health Serv Res 2007; 34:43–55
225. Hempel AG, Kownacki R, Malin DH, Ozone SJ, Cormack TS, Sandoval BG 3rd, Leinbach AE: Effect of a total smoking ban in a maximum security psychiatric hospital. Behav Sci Law 2002; 20:507–22
226. El-Guebaly N, Cathcart J, Currie S, Brown D, Gloster S: Public health and therapeutic aspects of smoking bans in mental health and addiction settings. Psychiatr Serv 2002; 53:1617–22
227. Lawn S, Pols R: Smoking bans in psychiatric inpatient settings? A review of the research. Aust N Z J Psychiatry 2005; 39:866–85