

Responding to question 3b: *What is known about the geography and epidemiology of pain in the population as a whole in the United States? Propose a research agenda for what is unknown.*

Pain is greatly under-treated in the United States, I was taught in medical school. This is a very important issue, and I welcome this opportunity to review the literature on what is known about the geography and epidemiology of pain in the United States and to propose a research agenda for what is unknown. The primary source that I will rely on is a collection of papers published in 1999 by the International Association for the Study of Pain called the *Epidemiology of Pain* edited by Crombie et al. To my knowledge, this was the first work of its kind to bring together these issues. A chapter also by the same name is part of the forthcoming 2006 *Wall and Melzack's Textbook of Pain*.

In order to address this question, some important terminological clarification is needed. The question asks about “the geography and epidemiology of pain” in the US population. The terms “geography”, “epidemiology”, and “pain” all need to be defined with sufficient clarity and accuracy in this context before we can proceed.

Firstly, let's investigate what is meant by “epidemiology.” The commonly accepted definition for epidemiology is: “the study of the distribution and determinants of health related states or events in a specified population and the application of this study to the control of health problems” (Last 1988). In the context of this question, the health related states are pain states and the health related events are painful events. The population in question is the United States population. Epidemiological investigation of pain states and painful events in the United States population would, by definition, reveal something about the distribution of pain states and events in the population, the causal determinants of those states and events, and shed light on how best to control or prevent

these states. Another way to look at this is given by Von Korff (1999) who elucidates three perspectives that epidemiological research into pain provides: a population perspective, which describes incidence and prevalence of pain; a developmental perspective, which focuses on the dynamic nature of pain states over time; and an ecological perspective, which examines how social, environmental, and host susceptibility influence pain (p.7).

Secondly, what is meant by “geography”? In this context, I feel safe to say that we are talking about the “medical geography of pain” rather than the political geography or economic geography of pain. This assumes some particular features about pain that I will describe later. Medical geography, using Frank Barrett’s definition, is the subdiscipline in geography that deals with “the analysis of the human-environmental relationship of disease, nutrition, and medical care systems in order to elucidate its interrelationships in space” (Barrett 1986, p. 27). In this context, the disease (or symptom, rather) is pain, and the medical care systems can be from the informal to the formal, i.e., everything from doctor-unassisted self-management of pain with non-prescription medicines to a pain management plan for an acute or chronic pain patient carried out by health care workers in a hospital setting. Since geography comes from a social science tradition, other topics that come under the medical geography of pain would include subjective experiences/narratives of pain, social factors influencing pain, cultural constructions of pain, and political or other kinds of obstacles for patient access to effective pain management. The human-environmental relationships with regards to pain are also broadly addressed in epidemiological perspectives already described.

Finally, what is “pain”? One definition adopted in 1986 by the International Association for the Study of Pain Subcommittee on Taxonomy is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (International Association for the Study of Pain Subcommittee on Taxonomy 1986). The key here is that, in this understanding of pain, the experience is wholly unpleasant and can often be correlated with actual or potential tissue damage. This is not ‘pleasant’ pain that one may enjoy experiencing (as in masochistic individuals, e.g.), and this does not refer to pain that is emotional, as in pain caused by the loss of a loved one or other close attachment. “Psychological processes”, however, are important “in the complex process of attending to, interpreting, and reacting to noxious stimuli” (Linton 1999, p.25). The now widely accepted gate-control theory of pain first proposed by Melzack and Wall in 1965 broadened our understanding of pain in that it recognized three main dimensions of pain: the sensory/physiological/nocioceptive, the affective/emotional/motivational, and the evaluative/cognitive dimension. Alterations in any of these three dimensions can change “the gate” that controls the subjective experience of pain—a raised gate leads to increased pain sensation and a lowered gate leads to decreased pain sensation. In recent years, laboratory investigations have shed light on the molecular basis of the gate-control theory. For example, a recent paper in *Nature* attributed stress-induced analgesia, a type of psychological gate control of pain, to the body’s endocannabinoid system whereas earlier papers had only shown endogenous opioid involvement (Hohmann et al. 2005). It goes without saying that the gate control theory of pain has opened up new vistas in the treatment of pain and in our understanding of why certain pain treatments work and others do not work.

There are many types of clinically definable pain states. For example, there is acute pain versus chronic pain (lasting 6 months or more) versus episodic pain. There is neurogenic pain, of which neuropathic pain is a special kind (the main difference being that neurogenic pain can be transient). Neuropathic pain can be broken down into central neuropathic pain and peripheral neuropathic pain. Then there are various kinds of specialized types of pain such as visceral pain, referred pain, cutaneous pain, somatic pain, phantom limb pain, neuralgias, allodynic pain, dyesthesias, spasms, and neuritis, to name a few. These can all be chronic, acute, or episodic and can occur as part of a chronic pain syndrome that may or may not be secondary to trauma, and so forth.

Given these three definitions of ‘epidemiology’, ‘geography’ and ‘pain’, the question—what is known about the geography and epidemiology of pain in the United States population as a whole?—becomes a very vast issue. To help make this approachable, I will interpret the “United States population as a whole” to mean that the focus of this question is on the WHOLE population, rather than on subpopulations that share particular defining characteristics. But since the population as a whole is comprised of numerous subpopulations, it may be impossible to avoid subpopulation-level descriptions. Indeed, it may be true that many of the population samples that have been studied thus far epidemiologically and geographically in terms of pain can only provide data that is generalizable to particular subpopulations instead of to the population as a whole. Furthermore, in the first part of the question, I will focus mainly on the incidence and prevalence in the population of pain conditions, but I will propose a new research agenda that focuses on treatment.

In this section, I will present in tabular format a sampling of what is known about the incidence and prevalence of pain in the US population.

Pain type studied	Sample description	Sample Characteristics	Generalizable to US population	Reference
Migraine	20,000+ persons aged 12-80; representative US sample; 1989	17.6% females and 5.7% males had experienced a migraine headache in the prior year; prevalence in the lowest income group (less than \$10,000) was more than 60% higher than in the two highest income groups (greater than or equal to \$30,000)	Yes, 8.7 million females and 2.6 million males suffer from migraine headache with moderate to severe disability. Of these, 3.4 million females and 1.1 million males experience one or more attacks per month	Stewart et. al (1992)
Frequent headaches	In Baltimore County, Maryland, 13 343 individuals 18 to 65 years of age were selected by random	The overall prevalence of frequent headache was 4.1% (5.0% female, 2.8% male; 1.8:1 female to male ratio). Highest prevalence in lowest educational category. Of these >1/2, chronic tension type headaches and >1/3 migrainous features	Yes, ~7 million adults in the United States suffer from frequent headaches (at least every other day)	Sher et al. (1998)
Trigeminal neuralgia and glossopharangeal neuralgia	Rochester, MN: 1945-1984		Yes, TN vs. GN: 4.7 vs. 0.8 per 100,000 pop	Katusic (1991)
Back pain	HMO pop in Seattle, n= 1016	Prior six-month prevalence: 41%. Higher among women at younger ages and increased steadily with age in men		Von Korff et al. (1988)
Chest pain	Same as above	Prior six-month prevalence: 12%; similar rates in males and females	?	Same as above
Temporomandibular	Same as above	Prior six-month	?	Same as above

disorder pain		prevalence: 0-8% in males, depending on age and 1-18% in females; both peak in 25-44 age range		
Chronic widespread pain	3006 persons randomly selected in Wichita, KS households	Young adulthood: 5% in men; 10% in women; Age 50-60: peaks: 22% in women, 12% in men	?	Wolfe et al. (1995)
Fibromyalgia	follow-up from above sample	7% peak prevalence in women ages 60-70; 4-5% in women ages 40-50	?	Same as above
Juvenile arthritis	n=17110; USA pop; age 0-8		Point prevalence: 460 per 100,000 pop	Newacheck et al. (1992)
Sickle Cell pain	Same as above		Point prevalence: 120 per 100,000 pop	Same as above
Phantom Limb pain	Various samples consisting of amputees	53%-72% for amputees	No	Kalauokalani and Loeser, 1999
Central Post-Stroke Pain	Various		Incidence: 16 per 100,000; Prevalence: 40 per 100,000	Vestergaard et al. (1999)
Neck pain	USA, Newspaper workers, n=900	Over 12 mo period, prevalence = 46%		Rosecrance et al. (1992)
Shoulder pain	Random sample, 25-74 yo, USA, n=6913	By questionnaire, 6.7% prevalence; by physical examination, 3.0%		Cunningham et al. (1984)
Knee pain	U.S. Probability sample: n=6913 ; age: 25-74 yo	Greater than 1 month Sx; past 1 year prevalence: 10.2%	Yes	National Center for Health Statistics (1979)

In addition to these data on incidence and prevalence of pain conditions gleaned from cross-sectional surveys and cohort studies, there is other epidemiological information that is known about the causal factors in many of these pain states. In addition,

epidemiologists have investigated clinical epidemiological issues such as co-morbid conditions, outcome, prognosis, etiology, treatment, prevention, diagnosis, costs, and policy implications of pain.

However, Crombie identifies several unknown horizons that can be addressed through geographic and epidemiologic studies. He writes that “insight from clinical and animal studies” can “stimulate comparisons among populations and among different groups within a society” (Crombie 1999, p.2). “But,” elsewhere, Crombie et al. add, “at present there is little connection between laboratory and clinical findings and the types of theories that can be investigated in epidemiological studies. We need insights that will foster research at the population level. The challenge is to synthesize the findings from basic research to provide causal mechanisms that can be tested in epidemiological studies” (Crombie et al., p. 21) While these authors are writing in terms of improving our knowledge of risk-factor epidemiology related to pain states, their observations are equally applicable to geographic and epidemiological studies assessing the nature and effectiveness of novel or emerging analgesic modalities for the treatment of pain, such as cannabis therapeutics.

Many pain conditions are well treated with opioid analgesia. However, there are several downsides associated with opioid therapy such as tolerance, dependence, stupor, and adverse GI side effects. In addition, in some chronic pain conditions, particularly migraines and neuropathic pain, opioids have generally been found to be unhelpful and, in the case of migraines, can produce a hyperalgesic effect (Russo 2004). Recently, cannabis and cannabinoids have (re)started being used clinically in the treatment of neuropathic pain, particularly peripheral neuropathies experienced by patients with

multiple sclerosis. Sativex, an oromucosal sublingual spray that is a whole plant cannabis medical extract (1:1 combination of two cannabis strains with high THC and high CBD content) has been approved for this indication and is being prescribed in Canada, Spain, and soon in the UK. Since this is a relatively new form of analgesia (despite the documented 4000 year old history of cannabis in treatment of migraine), many questions remain about the nature of cannabis-induced analgesia. Head-to-head clinical trials with opiates are needed, for example.

What is the nature of cannabis therapy? Ethan Russo has proposed the possibility of congenital or acquired syndromes that he calls “clinical endocannabinoid deficiencies” such as IBS, fibromyalgia, and migraine that display common clinical, biochemical and pathophysiological patterns; this may explain why administration of exogenous cannabis-based therapies is efficacious in some patients with these conditions. In terms of pain analgesia, some anecdotal reports suggest that cannabis therapy can synergistically potentiate the analgesic effects of opiate therapy for chronic pain and thereby prevent or stabilize patients’ tolerance to opiate therapy. Others have reported discontinuance of opiate therapy all together in favor of cannabis analgesia. Dr. Lester Grinspoon, a Harvard psychiatrist who has written extensively about cannabis therapeutics, claims that many who use cannabis for somatic pain relief “don’t talk much about the high” (*Stoned* 1998). Why would users experience a diminished psychological effect? Is an endocannabinoid-mediated gate control mechanism involved? Recent laboratory research into the mammalian endocannabinoid system has shown that this system regulates a wide variety of physiological functions. Just as the sympathetic nervous system regulates the ‘fight or flight’ response, the endocannabinoid system helps to

regulate 'Relax, Eat, Rest, Forget and Protect' functions (Petrocellis et al. 2004). The forgetting function is most intriguing in that it concerns particularly the extinction of aversive memories (*ibid.* and Mariscano 2002). Might cannabis-based analgesia be helping to treat pain through this mechanism? As Linton et al. point out in their paper on psychological factors involved in pain, "Even if a psychological variable is not causally linked to a pain problem, it might be helpful in controlling or alleviating the pain. Relaxation training, for example, often provides pain relief, even though muscle tension may not be the cause of the pain" (p.26). Perhaps the aversive memory extinction effect that comes with agonism of the endocannabinoid system is more important in treating pain related to traumatic injuries such as pain with PTSD secondary to emotional, psychological, sexual, or otherwise violent trauma.

These various observations about exogenous cannabis-based therapy and the endocannabinoid system can be used to form the basis of a new research agenda regarding cannabis and cannabis-based therapeutics for pain. How many users of cannabis use it to treat chronic pain? Which conditions? PTSD pain? Fibromyalgia? Migraine? Failed Back Surgery Syndrome? Cancer pain? Ehler-Danlos syndrome? MS pain? Of those who use cannabis medicinally, how many have discontinued or reduced opiate consumption as a result? How many have not increased opiate consumption? Might this be evidence of opiate + cannabis synergism in analgesia in addition to minimization of opiate tolerance? How do people experience pain relief through cannabis? Is it true that people who use cannabis for somatic ailments don't talk much about the "high", as Dr. Grinspoon asserts? What functions of the endocannabinoid

regulatory system are exogenous cannabinoids interacting with in order to diminish which aspects of the subjective pain experience?

Clinical epidemiological and medical geographic methods can be used to help answer these questions. Target patient populations to study through cross-sectional and cohort studies would be Sativex-using pain patients or whole-plant medical cannabis users. Given that various geographic locations have instituted markedly different policies with regards to the access of medical cannabis, community-trial like studies can be used to assess the impact of medical cannabis policies on pain outcomes of similarly matched pain patient populations residing in locations with differing policies in place. For example, some patients reside in places where no safe access policies are in place, and others reside in places where access is very good (Aggarwal et al. 2005). Ultimately, learning from successful self-care behaviors such as self-administration of cannabis for analgesia would help to guide tertiary prevention strategies for pain. Self-care is key because, in the end, chronic pain management is left to the individual patient. No one else can truly experiences his or her pain. Just as epidemiological methods can help to look at cross-cultural experience of pain, they can also be used to look at the unique nature of cannabis-based pain relief.

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