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*“Researchers are responsible for the ethical conduct of research conducted by them and  
by others under their supervision or control.”*

Tangney, 2000

**INTRODUCTION**

As the above quote clearly highlights, it is the responsibility of researchers and research supervisors to be certain that their research staff and students assistants are very familiar with all of the ethical principles and current standards relevant to the research they are conducting. Indeed, they must take an active role in being certain that their research staff and students complete appropriate training in these ethical principles and standards, and how they apply them to the research context in which they are working. This is especially important in areas in which there may be physical harm such as chronic pain research.

During the past decade, there has been a great increase in research of chronic pain, with breakthroughs in better understanding its etiology, assessment, and treatment (1,2). Obviously, much of this research was conducted using humans and animals as subjects. As a consequence, there were a number of ethical issues that investigators have to be cognizant of when conducting their studies. In this chapter, we will discuss such ethical issues in three major areas: (i) laboratory research with human subjects; (ii) laboratory research with animals; and (iii) translating these laboratory research findings to “real world” applications in the clinical treatment arena.

**LABORATORY RESEARCH WITH HUMAN SUBJECTS**

There has been a long history in psychology of using experimentally induced pain (such as the administration of electric shock) as both independent and dependent variables (3). For example, the presence/absence of electric shock (an independent variable) has been used to evaluate the effects of pain on learning and other behaviors. Also, the effects of perceived control on pain threshold/tolerance, using electric shock or other painful stimuli as the dependent variable, have also been investigated. As a result of a plethora of such research studies that were not

designed to evaluate pain per se, a great deal of adjunctive information was nevertheless gathered about what biopsychosocial factors affect pain and, vice versa, how pain affects various biopsychosocial factors. For example, a number of important findings concerning pain were revealed, such as gender and ethnic differences in pain threshold/tolerance as well as emotional reactivity to pain; placebo effects on pain reactivity; relationships among pain, anxiety and depression; effects of perceived control and predictability on psychophysiological responses to pain; and how pain affects the hypothalamic–pituitary–adrenal axis (3), to name a few areas.

In the “early days” of such psychological research (i.e., the 1960s and 1970s), subject safety and ethical issues were not carefully monitored or controlled by Institutional Review Boards (IRBs). In fact, as Vanderpool (4) noted in his review of the history of research ethics and guidelines, biomedical researchers in the United States resisted ethical and regulatory oversight of their investigations between 1946 and 1966. It was not until a landmark article by Beecher (5), published in the *New England Journal of Medicine*, which included an “expose” of 22 examples of unethical research conducted between 1948 and 1965, and in which the health and life of the research subjects involved was investigated, did the federal government become involved in research ethics. More responsibility to carefully monitor research was demanded of IRBs. However, as more awareness developed concerning the improper use and deception of research subjects, pressure was brought to bear by federal and state agencies to protect the safety and rights of such subjects. As a result, there developed the demand for all federally funded research supported by agencies such as the National Institutes of Health and the National Science Foundation, to be carefully reviewed for subject safety by IRBs. Moreover, professional organizations such as the American Psychological Association (APA) developed ethical guidelines for research, directly addressing issues such as informed consent to research and deception in research. For example, in terms of informed consent to research, the APA Ethics Code (8.02) specifically states the following:

1. When obtaining informed consent as required in Standard 3.10, Informed Consent, psychologists inform participants about (1) the purpose of the research, expected duration, and procedures; (2) their right to decline to participate and to withdraw from the research once participation has begun; (3) the foreseeable consequences of declining or withdrawing; (4) reasonably foreseeable factors that may be expected to influence their willingness to participate such as potential risks, discomfort, or adverse effects; (5) any prospective research benefits; (6) limits of confidentiality; (7) incentives for participation; and (8) whom to contact for questions about the research and research participants’ rights. They provide opportunity for the prospective participants to ask questions and receive answers.
2. Psychologists conducting intervention research involving the use of experimental treatments clarify to participants at the outset of the research (1) the experimental nature of the treatment; (2) the services that will or will not be available to the control group(s) if appropriate; (3) the means by which assignment to treatment and control groups will be made; (4) available treatment alternatives if an individual does not wish to participate in the research or wishes to withdraw once a study has begun; and (5) compensation for or monetary costs of participating including, if appropriate, whether reimbursement from the participant or a third-party payer will be sought [Standard 8.02a, Informed Consent to Research (6)].

In terms of deception in research, the APA Ethics Code (8.07) explicitly states the following:

1. Psychologists do not conduct a study involving deception unless they have determined that the use of deceptive techniques is justified by the study's significant prospective scientific, educational, or applied value and that effective nondeceptive alternative procedures are not feasible.
2. Psychologists do not deceive prospective participants about research that is reasonably expected to cause physical pain or severe emotional distress.
3. Psychologists explain any deception that is an integral feature of the design and conduct of an experiment to participants as early as is feasible, preferably at the conclusion of their participation, but no later than at the conclusion of the data collection, and permit participants to withdraw their data (7).

As a result of these ethical guidelines, it is now more difficult to conduct research when pain is experimentally induced. Some have claimed that this has "handcuffed" them from conducting needed research on pain in humans, based upon promising findings from animal research studies. Others argue that such "handcuffs" are needed for subject protection.

## LABORATORY RESEARCH WITH ANIMALS

Ethical concerns about laboratory research with animals are based on the assumption that animals perceive and experience noxious information. Both philosophers and scientists have, until now, tended to focus only on the most basic responses to painful stimuli such as withdrawal and nursing behaviors as well as the mechanisms supporting these responses. This has fostered some rather simplistic views about the functions of pain sensations (8,9) that have, in turn, supported a polarized debate. On the one side are those who point to withdrawal and nursing behaviors in nonhuman animals as evidence that their pain systems are essentially no different from the human pain system. On the other side are those who point out that these responses can be implemented with mechanisms that provide little confidence for the attribution of conscious experiences. If one limits oneself to these kinds of behaviors, it is indeed hard to think of empirical studies that would depolarize this debate. Philosophers, in particular, have an unfortunate tendency to think that if they cannot imagine any relevant experiments to address a particular question, then none can exist. It is our belief that ethical concerns on laboratory research with animals are important, and that pain is present in nonhuman species. There is much potential for investigating functional aspects of the experience of pain, providing, we hope, a fertile middle ground in which sophisticated comparisons of different species can grow, as can continual development for guidelines concerning laboratory research with animals.

The Committee for Research and Ethical Issues of the International Association for the Study of Pain (IASP) has published ethical guidelines for research involving the use of conscious animals in experimental pain studies (10). The following are the guidelines that investigators should consider when performing such studies. These guidelines attempt to address factors related to the importance of performing research as well as the severity and duration of the pain stimulus.

1. It is essential that the intended experiments on pain in conscious animals be reviewed beforehand by scientists and laypersons. The potential benefit of

- such experiments to our understanding of pain mechanisms and pain therapy needs to be shown. The investigator should be aware of the ethical need for a continuing justification of such studies.
2. If possible, the investigator should try the pain stimulus on himself or herself; this principle applies for most noninvasive stimuli causing acute pain.
  3. To make possible the evaluation of the levels of pain, the investigator should give a careful assessment of the animal's deviation from normal behavior. To this end, physiological and behavioral parameters should be measured. The outcome of this assessment should be included in the manuscript.
  4. In studies of acute or chronic pain in animals, measures should be taken to provide a reasonable assurance that the animal is exposed to the minimal pain necessary for the purposes of the experiment.
  5. An animal presumably experiencing chronic pain should be treated for relief of pain, or should be allowed to self-administer analgesic agents or procedures, as long as this will not interfere with the aim of the investigation.
  6. Studies of pain in animals paralyzed with a neuromuscular blocking agent should not be performed without a general anesthetic or an appropriate surgical procedure that eliminates sensory awareness.
  7. The duration of the experiment must be as short as possible, and the number of animals involved kept to a minimum (10).

In addition to the outlined IASP guidelines, additional guidelines for the care and use of animals have been developed by the APA and various local, state, and federal agencies (10–16). The importance of such consideration is that if investigators do not accept that nonhuman species possess the capability of painful experiences, then laboratory research involving animals is inherently limited in its application to human pain.

### **Conscious Pain Experiences**

The extent to which animals (e.g., rats) provide a model of conscious pain experiences remains a matter of uncertainty among most pain researchers and controversy among others. It is relatively well known that nociception, the basic capacity for sensing noxious stimuli, is widespread in the animal kingdom. Even relatively primitive animals such as leeches and sea slugs possess functionally specialized mechanisms for sensing noxious stimuli (17). Vertebrate spinal cords play a sophisticated role in processing and modulating nociceptive signals, providing direct control of some motor responses to noxious stimuli and a basic capacity for Pavlovian and instrumental conditioning (18,19). Higher brain systems provide additional layers of association, top-down control, and cognition. In humans, at least, these higher brain systems also give rise to the conscious experiences that are characteristic of pain.

"Analogical" arguments are widely exploited in the animal welfare literature (8). Anatomical similarities, including the presence of nociceptors connected to a central nervous system, physiological similarities including the existence of endogenous opioids, and behavioral similarities such as withdrawal, vocalization, and "nursing" responses to injury, have all been cited to support the view that many nonhuman animals suffer from pain and thus deserve moral consideration and legal protection. Some of the authors working in this area acknowledge that there is room for doubt about the force of the argument by analogy, but they apply

the precautionary principle that it is better to err on the side of too much protection rather than too little (9,20). Other authors, however, place considerably more weight on the analogy argument, considering it to be firmly established scientifically that there are no significant differences between humans and many other animals in the capacity to feel pain. This conclusion is often bolstered by appeal to evolutionary continuity between the species (21,22).

The standard analogy arguments that have been advanced by many philosophers are not sufficient to overcome arguments that conscious experiences of any sort are beyond the reach of empirical investigation, and that there exists significant disanalogies between humans and other animals, which make it unlikely that the experiences of nonhuman animals are anything like the conscious experiences of humans. This is because the providers of these lists of similarities generally do not provide any theoretical reasons for connecting them to attributions of conscious pain. Specialized nociceptors are found in such relatively primitive organisms as sea slugs and leeches and, as such, do not provide strong grounds for attributing conscious pain to these organisms. Opioid systems are also widespread among animals. Many withdrawal responses, and even some forms of learning about noxious stimuli, can be accomplished by spinal cords without mediation by higher brain systems (19). If items on the list do not individually entail conscious experience of pain, it is not clear why satisfying multiple criteria should add up to conscious experience. Analogy arguments are vulnerable because, for all the similarities between humans and other nonhuman animals, there are dissimilarities that can be used to deny the inference to conscious pain in nonhumans (23). While human brains may be similar to animal brains at the level of gross anatomy and physiology, more fine-grained analysis reveals numerous differences. It is also open to critics to point out the many ways in which human behavior is not identical to the behavior of other animal species. Consequently, without an adequate framework for understanding the connection between the observed similarities and conscious pain, analogy arguments remain essentially weak.

A "functional" understanding of pain in the context of learning would provide a framework for assessing comparisons of anatomy, physiology, and behavior (8). Recent work on the sensory and emotional aspects of pain experiences in rats provides a context in which the functional roles of different components of the phenomenology of pain could be investigated with respect to anatomy (particularly the role of the anterior cingulate cortex), physiology (the effect of opioid substances), and behavior (avoidance of aversive contexts) (24–28). While the development of such a framework may not ultimately convince all skeptics, it may help to preempt skeptical and antiskeptical arguments that are based on overly simplistic ideas about the functions of pain. The aim is to chart a middle course between the excessively skeptical view that animal pain cannot be studied empirically and the overly credulous view that scientific investigation has already revealed that other animals (other mammals, at least) feel pain much as we do. The intent is not to show that rats experience pain consciously, but rather to suggest that an empirical research program based on a functional understanding of pain allows sophisticated comparisons to be drawn between the pain experiences of humans and those of other animals. The move from simple behavioral measures (stimulus-response) to more sophisticated operant behavioral techniques suggests additional methods for investigating the roles that different dimensions of painful experiences might play in higher order forms of learning. For example, is

long-term conditioning differentially affected by blocking the sensory and affective components of pain processing? Does treatment with morphine affect the ability of rats to learn about noxious stimuli? Would treated rats fail to learn associations between contextual cues and noxious stimuli, or is sensory awareness sufficient? Would the effect vary for different types of pain conditions (i.e., is sensory awareness sufficient for acute conditions but not chronic conditions?). Additionally, if given the choice, would rats learn to self-administer sensory and affective pain relief differentially?

A second topic of interest is motivational drives. Do animals experiencing food deprivation and pain simultaneously choose to eat, or does the pain drive supersede the hunger drive? Is their choice differentially affected by blocking sensory and affective components of pain processing? Furthermore, is the loss of pain affect associated with loss of affect in other behaviors (i.e., mating, predator/prey, and maternal behaviors)? Do losses of pain affect versus sensory pain experience differentially modify these behaviors? The ability to investigate such questions at a functional level of analysis opens the door to much more detailed analyses of the importance of these different aspects of painful experiences. It is also worth noting that the utility of these measures depends to a large degree on animals exercising choices in conditions in which they are not in so much pain as to be rendered immobile or dysfunctional. While the deliberate infliction of pain on another organism is always a matter of ethical and moral concern, the experiments we propose generally involve a degree of pain that would be consistent with good overall welfare. Furthermore, while informed consent is unattainable with nonhuman subjects and causes the animals' insertion into the experimental situation not to be regarded as voluntary, the use of operant conditioning techniques comes closer than other methods to giving the animal subjects voluntary control over their exposure to noxious stimuli within the experimental situation.

### **Recent Advances in Animal Pain Studies**

Recent advances in animal pain studies are beginning to make it possible to describe more precisely the roles played by different aspects of painful experiences. An understanding of how the unpleasantness of pain connects to the complex cognitive capacities of organisms would provide an explanatory framework that would allow behavioral evidence from a variety of species to be assessed. Of course, it is open to the more ideological skeptic to maintain that none of this tells us anything about the conscious nature of animal experiences, because all the anatomical, physiological, and behavioral evidence in the world is compatible with the complete absence of conscious experience. But this view applies just as much to the ability to investigate human experiences of pain as it does to nonhuman animals and, as such, provides no special barrier to our understanding of animal pain. Another kind of skeptic believes that outstanding differences in higher cognitive abilities such as language processing or theory of mind abilities are the crucial elements for understanding the nature of conscious experience. They may be correct, but no empirical method has been provided for testing the hypothesis that consciousness serves those functions. In contrast, novel behavioral techniques now make it possible to test an alternative class of hypotheses linking the phenomenology of painful experiences to specific motivational and learning functions. By manipulating dimensions of the painful experience, we stand to gain a more

detailed view of the complex relationship between behavior, mechanism, and experience, which, in turn, strengthens the basis for analogical comparisons of animals and humans. Ultimately, we can relate this information to address ethical issues in animal pain research.

### **TRANSLATING LABORATORY RESEARCH TO THE CLINICAL TREATMENT ARENA**

Traditionally, the “gold standard” assumed to provide the best evidence for the efficacy of a new treatment technique is the randomized controlled trial (RCT). In such a trial, subjects are randomly assigned to either an active treatment group (e.g., a new medication assumed to alleviate pain) or a control treatment group in which the attention and time spent by subjects with a clinician is the same as in the active treatment group. Subjects in a control treatment group are given a similar “medication” (in this case, an inactive placebo pill which looks like the active medication pill). Subjects in this latter group assume that they are actually being given the new active medication. Such RCTs can similarly be conducted comparing other active treatment techniques for reducing pain, such as cognitive-behavioral therapy, to inactive or placebo treatments such as nondirective psychotherapy in which the time spent in treatment is equal between groups. Many scientific journals will not accept treatment-outcome studies of new pain management techniques, even if they are based upon solid evidence from laboratory studies, unless they are RCTs.

Unfortunately, today there are some major ethical considerations that often prevent the use of an RCT methodology in many clinical trials, especially in the United States (29). Indeed, in an early review of this issue, O’Leary and Borkovec (30) pointed out that, when considering attention placebo-control groups, their use in many research projects may be “theoretically, methodologically, practically, and ethically unsound” (p. 823 Ref. 30). They stated that the theoretical and methodological problems in developing placebo groups include difficulties developing a truly “inert” treatment; the likelihood of a therapist not being able to accept or have any confidence in implementing a placebo condition for more than one or two sessions; and the probability that patients would drop out of a placebo group over time. Ethical considerations include the fact that placebos are inherently deceptive, and they deter the patient from seeking active treatment during the course of the experimental evaluation; when patients discover that they were given a placebo, they may feel angered that time was wasted at their expense, and, finally, subjects given a placebo will not improve and some may deteriorate, resulting in potential harm to the subject. This would seriously violate the ethical concern of the right to treatment. Moreover, Freedman (31) and Levine (32) have cogently reviewed significant bioethical concerns associated with placebo-control groups. In addition, the World Medical Association’s Declaration of Helsinki does not recommend the use of a placebo or no treatment control group, except in studies in which no proven prophylactic, diagnostic, or therapeutic methods exist (33). Fortunately, though, there are good alternatives to RCTs that can be used to demonstrate treatment efficacy (34). Concato et al. (35) have appropriately noted that the popular belief that only RCTs will unequivocally produce trustworthy results, and that all observational studies may be misleading, is not accurate. Concato and associates highlight the fact that the results of a well-designed observational study

(with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatments, relative to those in RCTs on the same topic. Even though an RCT can be viewed as a important benchmark to use in considering the validity of treatment-outcome results, many RCTs vary greatly in the degree of internal and external validity that make them less than "perfect" in nature. Fortunately, there are a host of other experimental designs that may be appropriately employed to yield important scientific data to help in delineating cause-effect relationships (e.g., quasiexperimental designs). Some may actually have greater internal or external validity than certain RCTs. Moreover, Heinsman and Shadish (36) have pointed out that a well-designed nonrandomized study can often yield a reasonable comparable effect size when compared with randomized designs. Thus, one should not be misled into accepting the argument that an RCT is the only research methodology available to produce scientifically acceptable treatment-outcome results. We must remember that the interpretation of results from any study, regardless of the research methodology employed, is an inferential process. The statement "unequivocal results or conclusions" can rarely be made in the scientific literature of chronic pain and clinical outcomes research.

#### **FUNDING ISSUES RELATED TO CHRONIC PAIN RESEARCH**

Of course, any discussion of ethical issues in chronic pain research must address the issue of potential conflicts of interest as to who funds such research. In studies with human subjects, much funding has been traditionally provided by the pharmaceutical industry, which has the most to gain, financially, from the development and sale of pain-reduction medications. For example, as an indication of the amount of monies involved in this endeavor, more than 312 million prescriptions for analgesics (137 million for opioids) are written each year (Merck Pharmaceutical, 2002, personal communication with Mark Williams). At the upper limits of costs for medication [\$21,500 (37)], the total cost could be as high as \$62.5 billion annually!

Because of the great financial incentives, there has been growing scrutiny of pain medications that may have possibly been prematurely "brought to market" before comprehensive clinical trials testing them for all potential negative long-term side effects. For example, the recent revelation of cardiovascular morbidity (mortality side effects of the new line of COX-2 inhibitors, such as Vioxx) has stimulated a storm of controversy about oversight weaknesses. This, in turn, has amplified earlier concerns and accusations that control of data from clinical trials is often in the hands of the sponsoring pharmaceutical company (which has the most financial gain and potential conflict of interest), and that interim reports and the statistical analyses of results are rarely performed by independent groups (38). Other ethical dilemmas involved in such industry-sponsored clinical trials research have also been voiced (39).

As a result of the above, there is now growing scrutiny of major conflicts of interest among investigators, universities, and any companies that collaborate in clinical trials of pain medications, in which the financial benefits to the companies are so large. In a number of articles, this issue of potential conflict, which appears to be endemic, has been revealed and strongly voiced (40,41). Changes in federal oversight guidelines are certain to follow.

## CONCLUSIONS

In this chapter, we have discussed important ethical issues faced by investigators conducting research on chronic pain. Three major areas were discussed: (i) laboratory research with human subjects; (ii) laboratory research with animals; and (iii) translating these laboratory research findings to “real world” applications in the clinical treatment arena. As was reviewed, there are different ethical and philosophical issues in each area. Potential financial conflicts of interest with companies that may be sponsoring this research were also highlighted. Accordingly, it is incumbent upon researchers, and their staffs, to obtain appropriate training in ethical principles and standards, and to recognize how these apply to research contexts in which they are working. Fortunately, there is now an array of sources that provide information about these ethical principles and standards. Some of these are listed below.

### Website Sources

1. American Psychological Association <http://www.apa.org/>
2. American Psychiatric Association <http://www.psyc.org/>
3. National Institutes of Health <http://www.nih.gov/>
4. National Science Foundation <http://www.nsf.gov/>
5. American Pain Society <http://www.ampainsoc.org/>
6. IASP <http://www.iasp-pain.org/>

### FURTHER READINGS

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). *The Belmont Report*. Washington, D.C.: Department of Health, Education, and Welfare.
- International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: The Council for International Organizations of Medical Sciences (CIOMS), 2002. [www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm). accessed august 23, 2006).
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