Published in final edited form as:
Int J Nurs Stud. 2013 September ; 50(9): 1283–1287. doi:10.1016/j.ijnurstu.2012.11.023.

Ethical and Legal Issues in Pain Research in Cognitively Impaired Older Adults

Todd B. Monroe, PhD, RN-BC,
JAHF & Atlantic Philanthropies Claire M. Fagin Fellow, School of Nursing, Vanderbilt University, Nashville, TN, USA, Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA, 461 21st Ave. South, Nashville, TN 37240, 615-686-0828, Fax 615-343-7711, todd.b.monroe@vanderbilt.edu

Keela A. Herr, PhD, RN, AGSF, FAAN,
Professor & Co-Director, John A. Hartford Center of Geriatric Nursing Excellence, Associate Dean for Faculty, College of Nursing, The University of Iowa, 306 CNB, 50 Newton Road, Iowa City, IA 52242, 319-335-7080 (0ffice), 319-335-7033 (Fax), keela-herr@uiowa.edu

Lorraine C. Mion, PhD, RN, FAAN, and
Independence Foundation Professor of Nursing, School of Nursing, Vanderbilt University, 461 21st Ave. South, Nashville, TN 37240, 615-343-7098, Fax 615-343-7711

Ronald L. Cowan, MD, PhD
Psychiatry Clerkship Director, Director, Psychiatric Neuroimaging Program, Scientific Director, Vanderbilt Addiction Center, Associate Professor of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Avenue South, Suite 3057, Nashville, TN 37212, Phone: 615-322-2303, Fax: 615-936-3563, ron.cowan@vanderbilt.edu

Research involving those with dementia is critical to informing best practices and improving the quality of their lives. Pain research in people with dementia is of particular interest because the prevalence of both dementia and painful conditions increases with age. Inadequate assessment and treatment of pain is well documented in this vulnerable population (Herr and Decker, 2004, Herr and Garand, 2001, Monroe and Carter, 2010, Monroe et al., 2012). Additional basic science pain research is critically needed to better understand how sensory impairments, such as pain, may alter mood or behavior in people with dementia or how the pathology of dementia itself may alter the sensory system (Monroe et al., in press; Nuffield Council on Bioethics, 2009). Because courts have found that poor pain management in older adults is neglectful (Furrow, 2001) and constitutes elder abuse (Rich, 2004), improper management of pain in older adults has legal ramifications.

Unfortunately, research that supports best practices for assessing and treating pain in the cognitively impaired is limited. Obstacles to research in older adults, including those with cognitive impairment, have been highlighted along with an urgent call for increased research to promote quality pain care for all older adults (Reid et al., 2011, Taylor et al., 2012). Importantly, the characteristic's of the researcher play a role in both ethical principles and legal implications of research involving people with dementia. Key personality traits such as

Correspondence to: Todd B. Monroe.

integrity, trustworthiness, and honesty are associated with a high degree of ethical research; while lack of knowledge about ethical and legal principles can be obstacles to good research outcomes (Alzheimer Europe, 2011).

Research involving older adults often excludes people with cognitive impairment (Taylor et al., 2012). An obvious reason for excluding cognitively impaired people in research is the application of the first ethical principle in the Belmont report (U.S. Department of Health & Human Services, 1979): respect for persons encompasses the treatment of individuals as autonomous beings and ensuring protection of vulnerable populations who may not be able to provide autonomous informed consent. However, not including those with cognitive impairment violates the ethical principle of justice, that is, people who are likely to benefit from research participation should not be systematically excluded. To address these ethical principles, Casarett (2003) recommended that during the planning phase of any study that includes cognitively impaired people, investigators consider how issues regarding informed consent, recruitment, and surrogate involvement affect sample size, eligibility, and measurement (p. 25). Additionally, investigators should consider enrolling and including people who are in all stages of dementia (Alzheimer Europe, 2011, Nuffield Council on Bioethics, 2009).

Pain research in people with dementia can pose additional ethical challenges because the research may have no direct benefit to the subject (i.e., beneficence) and the research team must be clear in communicating the study's therapeutic intent, or lack thereof (Dresser, 2000). A well-designed study examining pain in cognitively impaired populations should demonstrate consideration of the ethical guidelines for pain research in people with dementia provided by recognized organizations such as the National Bioethics Advisory Commission (1998), the International Association for the Study of Pain (2012), the American Pain Society (2012), and the Alzheimer's Association (2007).

Aims

The aims of this paper are to review ethical challenges and related legal implications that can occur in pain research in cognitively impaired populations and to present potential solutions when preparing study protocols. For the purposes of this report, the broad term cognitive impairment includes people with borderline to very severe cognitive impairment (Morris et al., 1994). The terms cognitive impairment and dementia are used interchangeably.

Approach

Using the framework outlined by Dresser (2000), a discussion is presented on five ethical challenges with legal implications that are central to dementia research: (1) determining capacity, (2) surrogate decision making, (3) assessment of risk, (4) potential benefits, and (5) measures to increase study understanding. Our discussion includes recommendations for research in people with dementia that have been established by the International Association for the Study of Pain, American Pain Society, National Bioethics Advisory Commission , Alzheimer-Europe, Nuffield Council on Bioethics, and the Alzheimer's Association. Examples and suggestions for addressing each ethical challenge are presented with a particular focus on legal issues in the United States.

Determining Capacity

The foundations of capacity determination were identified in the Nuremberg Code (Hurren, 2003) and in the Declaration of Helsinki (World Medical Association, 2000). In 1947 the Nuremberg Code helped to establish the basic components of ethical research. The first

component of the Code requires a participant have the capacity to volunteer to engage in research (Shuster, 1997). In 1964, the Declaration of Helsinki stated that research participants must be volunteers and they must be informed about the purpose of the research (World Medical Association, 2000). Determining cognitive capacity involves the person's ability to communicate the choice, the understanding of important information, such as the risks and the benefits, and the ability to explain the components of the research, such as the task-specific procedures involved (Appelbaum and Grisso, 1988). Clearly, this presents a challenge for the conduct of research with cognitively impaired older persons. When people are cognitively impaired and unable to provide consent, relatives or verified friends should be able to make choices for those lacking capacity (Alzheimer Europe, 2011).

Members of institutional review boards closely examine study protocols that include vulnerable populations to ensure adequate protections (Casarett, 2003) and may request that capacity screens be performed on both subjects and controls. A person is considered capable of providing consent unless proven otherwise; thus, investigators should preemptively include a tool and a plan to screen for capacity with their research proposal (Alzheimer Europe, 2011). One brief tool is the University of California San Diego Brief Assessment of Capacity to Consent (Jeste et al., 2007). This tool is a 10-item scale with acceptable internal consistency (Cronbach's alpha 0.76 to 0.77), inter-rater reliability (r=0.84 to 0.98), concurrent validity, high sensitivity (89%), and excellent specificity (100%). The capacity tool takes 5 minutes to administer with each item having possible scores of 0=incorrect answer, 1=partially correct answer, and 2=correct answer for a maximum score of 20. According to the tool developers, people with scores greater than 14.5 are likely to have the capacity to consent. An example item from the tool is, “Do you have to be in this study if you do not want to participate?” A response of “no” would receive a score of 2. Recently, an expert panel recommended that when using an experimental pain paradigm a “basic rule of thumb” is that older adults with a Mini Mental State Exam (Folstein et al., 1975) score ≥ 18 can “generally provide meaningful responses” about pain sensation (Hadjistavropoulos et al., 2009). Regardless of the score on any single cognitive assessment tool, avoid making assumptions about the person’s ability to consent or to report pain (Herr, 2011). In summary, there is no universal definition of *lacking capacity* (Mayo and Wallhagen, 2009) and investigators should screen for capacity using a systematic approach. One approach is to combine objective data, based on a standardized screening tool, with subjective data, based on the investigator’s clinical judgment (Jansen et al., 2004).

Surrogate consent and subject assent

Surrogate consent and subject assent (when possible) should both be obtained in research involving people with dementia (Beck and Shue, 2003). If a participant lacks capacity, legal surrogate consent must be obtained. Laws vary on who can provide legal surrogate consent (Mayo and Wallhagen, 2009) and investigators should work with members from their local institutional review board or ethics committee to determine the legal consenting procedures.

Dresser (2000) found that surrogate consent could be obtained from legal health care proxies or, if none exists, caregivers such as relatives or close friends may provide consent. Karlawish (2003) described a caregiver as someone who is both “socially and institutionally sanctioned”. The National Bioethics Advisory Commission (1998) recommended that surrogate consent be obtained in research involving more than a minimal risk to the person lacking capacity. Dresser (2000) summarized findings from several organizations and concluded that with surrogate consent it is reasonable for persons who lack capacity to participate in research except in high-risk studies with no individual benefit. However, the absence of perceived direct benefit should not prevent investigators from including people with dementia in research (Alzheimer's Association, 2011).

Because the degree of dementia varies among participants, in those who lack capacity but are able to communicate, participant assent should be obtained. To obtain assent from someone requires that the investigator explain the basic components of the study in clear simple language allowing the subject to agree or decline to participate (Jansen et al., 2004). In cases where subject assent is obtained, legal surrogate consent must also be obtained.

Further research is needed in identifying how advanced decisions regarding participation in research can be made (Nuffield Council on Bioethics, 2009). In rare instances individuals may have a research advance directive or *advanced consent* in which they list the types of research in which they would or would not participate (Karlawish, 2003). For example, when planning a longitudinal prospective study, people at risk for developing cognitive impairment could provide advanced consent for study procedures that will occur some time in the future.

Assessment of risk

People with dementia, and their caregivers, must be informed of the potential risks of participating in research (Alzheimer Europe, 2011, Nuffield Council on Bioethics, 2009). However, determining when people with dementia lose the ability to understand the risks associated with research can be difficult (Karlawish, 2003). The Code of Federal Regulations or *Common Rule,* 46.102 (Department of Health and Human Services, 1991) states that, “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” One method proposed to assess for an appropriate level of risk is the “net risk” test for participant interventions required in research (Wendler and Miller, 2007). Here “net risk” means that the risk of harm does not exceed the potential benefit. In people with diminished capacity, a term used to describe appropriate “net risk” involving minimal risk procedures is “minor increase over minimal risk” (Dresser, 2000, Wendler and Miller, 2007). For example, in anticipation of local review board or ethics committee concerns, investigators using an experimental pain delivery paradigm may explain that the pain caused by study procedures has been reported to be less than the level of pain caused by most cases of osteoarthritis among people who are cognitively intact. Since many people with dementia have osteoarthritis, this reasoning may help to explain that the level of risk in the proposed research is similar to what many older adults with osteoarthritis would normally experience.

When painful treatments or procedures are one component of the research design involving people with dementia, additional safeguards are required. A provocative example of an additional safeguard proposed by Bellieni et al. (2012) is the appointment of an independent review committee for studies involving greater than minimal risk. They speculate that the institution’s review board or ethics committee may be incapable of providing an unbiased atmosphere since board or committee members are usually employed by the institution and not by the subjects (p.429). Regardless of the level of risk inherent in a study (i.e. minimal, minor increase over minimal, or greater than a minor increase over minimal), any subject dissent to participate must be respected (Karlawish, 2003).

Potential benefits

Two types of benefits are considered in research, direct and indirect. Direct benefits result from the potential therapeutic effects of the clinical research, such as experiencing decreased pain. Indirect benefits include opportunities for social interaction and positive feelings about contributing to medical progress (Dresser, 2000). Since the primary purpose of many research proposals is to advance knowledge and not to provide treatment—therefore offering no direct benefit to participants—safeguards must be in place to protect subjects with limited

capacity. According to the European Alzheimer's Association (2010), research in people with AD that does not have a direct therapeutic benefit is acceptable if:

> The research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same category or afflicted with the same disease or disorder or having the same condition.

Prior to enrollment, investigators should explain that the proposed research may have no direct benefit and participants and/or their caregivers should be able to clearly articulate when participation in the proposed research has no direct benefit to them. Studies with no direct benefit may increase the possibility of dignitary harm, i.e. lack of respect for personal rights (Goldfarb, 2005). To help reduce the dignitary harm resulting from inclusion in studies with no direct benefit, investigators should determine ways to share study results with subjects and caregivers (Karlawish, 2003).

Measures to increase study understanding

In a participant with limited capacity or in surrogates making decisions for those with dementia, obtaining indication of understanding about the research is legally and ethically necessary. To accomplish this, the institutional review board or ethics committee usually require that investigators develop a basic script explaining the purpose of the study, potential risks, potential benefits, and the procedures. In our experience, simplifying the narrative, using pictures and repeating the information can increase understanding and the likelihood of obtaining subject assent and/or surrogate consent.

Investigators should carefully educate participants and caregivers on the differences between clinical care and research (Dresser, 2000). For example, clinical care may be targeted at reducing pain while research may involve the application of an experimental pain stimulus. To increase understanding about the level of discomfort that a participant will experience, investigators may invite members from the institutional review board or ethics committee to feel any experimental pain stimulus. Also, investigators can include provisions for the legal surrogate, family, friends, or caregivers to experience the pain stimulus. Second, because the institutional review board includes members from outside of the scientific community, using everyday language in study applications will provide explanations of pain that most can understand. When using thermal heat stimuli for example, 50° Celsius is about the temperature of a cup of hot coffee (De Jong et al., 1972), while 41° Celsius is the temperature of an average hot bath (Brann, 2012). Mechanical pressure pain could be described as a clothespin applied to the tip of the finger over a defined period of time. Other painful stimuli used may be described as pain that would occur during routine clinical care such as an intravenous stick, a flu shot, or by an inflated blood pressure cuff.

Guidelines for pain research in people with dementia

In addition to the components outlined above, pain research in people with dementia should conform to the American Pain Society's (2012) and The International Association for the Study of Pain's (2012) ethical principles of human research. Both of these organizations state that people who cannot provide consent should only be included in the research when their involvement is *essential* to the goals of the research. As aforementioned, when this occurs, legal surrogate consent should be obtained. The *minimum* intensity of pain required to achieve the goals of the study should be established beforehand and this level of intensity should not be exceeded during the course of the study. Second, the level of pain should never exceed the subject's pain tolerance limit. Third, when possible, participants should be

able to stop the painful stimulus at anytime. Fourth, pain medication should be available in clinical pain studies or those that use a placebo treatment (Bellieni et al., 2012). Last, any research involving people with dementia should clearly state a legal obligation to pay for any injuries resulting from participation in research (Eriksson, 2010).

Conclusions

A foundation for addressing ethical challenges and related legal implications in pain studies in people with dementia has been presented. Many of these suggestions could be tailored to experimental paradigms addressing clinical problems other than pain. While the current report used pain as an exemplar, research that includes people with cognitive impairments is needed in many areas in order to help inform the care of older adults. Investigators who study people with cognitive impairment must be vigilant to include multiple safeguards to protect all parties. Taking the time to apply additional safeguards should not prevent investigators from including people with dementia in their research. The importance of including cognitively impaired people in research is clear and failing to do so may lead to greater suffering through lack of evidence to support best practice recommendations in this vulnerable group. If results demonstrate differences in response to experimental treatments, targeted intervention strategies might be tailored to inform the future clinical management of people with dementia.

References

Alzheimer Europe. Involving people with dementia in research. 2010. from http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Involving-people-with-dementia-in-research

Alzheimer Europe. [Retrieved July 30, 2012] Ethics of dementia research. 2011. from http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Ethics-of-dementia-research/The-dementia-ethics-research-project-fragment-1

Alzheimer's Association. Ethical issues in dementia research. 2007. from http://www.alz.org/national/documents/statements_ethicalissues.pdf.

Alzheimer's Association. [Retrieved October 17, 2009] Alzheimer's disease facts and figures. 2011. from http://www.alz.org/national/documents/report_alzfactsfigures2011.pdf

American Pain Society. [Retrieved Janurary, 30, 2012] Ethical principles for pain-related clinical research. 2012. from http://www.ampainsoc.org/about/ethics.htm

Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. New England Journal of Medicine. 1988; 319(25):1635–1638. [PubMed: 3200278]

Beck C, Shue V. Surrogate decision-making and related Issues. Alzheimer Disease and Associated Disorders. 2003; 17:S12–S16. [PubMed: 12813219]

Bellieni CV, Rocchi R, Buonocore G. The ethics of pain clinical trials on persons lacking judgment ability: Much to improve. Pain Medicine. 2012; 13(3):427–433. [PubMed: 22313615]

Brann, J. [Retrieved April 17, 2012] The benefits of varying bath water temperatures. 2012. from http://www.womenshealthcaretopics.com/bn_bodysoul_Benefits_Varying_water_temperatures.htm

Casarett DJ. Assessing decision-making capacity in the setting of palliative care research. Journal of Pain and Symptom Management. 2003; 25(4):S6–S13. [PubMed: 12691692]

De Jong UW, Day NE, Mounier-Kuhn PL, Haguenauer JP. The relationship between the ingestion of hot coffee and intraoesophageal temperature. Gut. 1972; 13(1):24–30. [PubMed: 5060664]

Common Rule. Federal policy for the protection of human subjects. Notices and rules, Federal Reg 1991. 1991; 56:28003–28032. C.F.R.

Dresser R. Dementia research: Ethics and policy for the twenty-first century. Georgia Law Review. 2000; 35:661–678. [PubMed: 15119320]

Eriksson S. On the need for improved protections of incapacitated and non-benefiting research subjects. Bioethics. 2010

Folstein M, Folsten S, McHugh P. Mini-mental state: A practical method for grading the cogntive state of patietns for the clinician. The Journal of Psychiatric Research. 1975; 12:189–198.

Furrow B. Pain management and provider liability: No more excuses. The Journal of Law and Ethics. 2001; 29(1):26–50.

Goldfarb N. Clinical trial injuries: Will your client lose his/her medical practice? Law Journal Newsletters. 2005; 22(6)

Hadjistavropoulos T, Marchildon GP, Fine PG, Herr K, Palley HA, Kaasalainen S, Béland F. Transforming long-term care pain management in North America: The policy–clinical interface. Pain Medicine. 2009; 10(3):506–520. [PubMed: 19254336]

Herr K. Pain assessment strategies in older patients. The Journal of Pain. 2011; 12(3, Supplement):S3–S13. [PubMed: 21396599]

Herr KA, Decker S. Assessment of pain in older adults with severe cognitive impairment. Annals of Long Term Care. 2004; 12(4):46–52.

Herr KA, Garand L. Assessment and measurement of pain in older adults. Clinics in Geriatric Medicine. 2001; 17(3):457–478. [PubMed: 11459715]

Hurren, E. [Retrieved August, 8, 2012] Patients' rights: from Alder Hey to the Nuremberg Code. 2003. from http://www.historyandpolicy.org/papers/policy-paper-03.html

International Association for the Study of Pain. [Retrieved January, 30, 2012] Ethical guidelines for pain reserach in humans. 2012. from http://www.iasp-pain.org/AM/Template.cfm?Section=Research_in_Humans

Jansen LA, Lebovits A, Brushwood DB. Of self-determination, care by proxy, and new techniques. Pain Medicine. 2004; 5(1):94–97. [PubMed: 14996241]

Jeste D, Palmer B, Applebaum P, Golshan S, Glorioso D, Dunn L, Kraemer H. A new brief instrument for assessing decisional capactiy for clinical research. Archives of General Psychiatry. 2007; 64(8):966–974. [PubMed: 17679641]

Karlawish JHT. Conducting research that involves subjects at the end of life who are unable to give consent. Journal of Pain and Symptom Management. 2003; 25(4):S14–S24. [PubMed: 12691693]

Karlawish JHT. Research involving cognitively impaired adults. New England Journal of Medicine. 2003; 348(14):1389–1392. [PubMed: 12672869]

Mayo AM, Wallhagen MI. Considerations of informed consent and decision-making competence in older adults with cognitive impairment. Research in Gerontological Nursing. 2009; 2(2):103–111. [PubMed: 20077971]

Monroe T, Carter M. A retrospective pilot study of African-American and Caucasian nursing home residents with dementia who died from cancer. Journal of Pain and Symptom Management. 2010; 40(4):e1–e3. [PubMed: 20817471]

Monroe T, Carter M, Feldt K, Tolley B, Cowan R. Assessing advanced cancer pain in older adults with dementia at the end-of-life. Journal of Advanced Nursing. 2012; 68(9):2070–2078. [PubMed: 22272816]

Monroe T, Chin L, Gore J, Mion L, Cowan R. Pain research in people with Alzheimer's disease: Potential applications for psychophysical and neurophysiological studies. Journal of Geriatric Psychiatry and Neurology. (In press).

Morris J, Brant E, Fries D, Mehr C, Phillips C, Mor V, Lipsitz L. MDS cognitive performance scale. Journal of Gerontology. 1994; 49(4):m174–m182. [PubMed: 8014392]

National Bioethics Advisory Comission. [Retrieved December, 30, 2011] Research involving persons with mental disorders that may affect decisionmaking capacity. 1998. from http://bioethics.georgetown.edu/nbac/capacity/TOC.htm

Nuffield Council on Bioethics. [Retrieved July 30, 2012] Dementia: ethical issues. 2009. from http://www.nuffieldbioethics.org/dementia

Reid MC, Bennett DA, Chen WG, Eldadah BA, Farrar JT, Ferrell B, Zacharoff KL. Improving the pharmacologic management of pain in older adults: Identifying the research gaps and methods to address them. Pain Medicine. 2011; 12(9):1336–1357. [PubMed: 21834914]

Rich BA. Thinking the unthinkable. Journal of Pain and Palliative Care Pharmacotherapy. 2004; 18(3): 63–74. [PubMed: 15364633]

Shuster E. Fifty years later: The significance of the Nuremberg Code. New England Journal of Medicine. 1997; 337(20):1436–1440. [PubMed: 9358142]

Taylor JS, DeMers SM, Vig EK, Borson S. The disappearing subject: Exclusion of people with cognitive impairment and dementia from geriatrics research. Journal of the American Geriatrics Society. 2012; 60(3):413–419. [PubMed: 22288835]

U.S. Department of Health & Human Services. [Retrieved August, 7, 2012] The Belmont Report. 1979. from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

Wendler D, Miller FG. Assessing research risks systematically: the net risks test. Journal of Medical Ethics. 2007; 33(8):481–486. [PubMed: 17664310]

World Medical Association. World medical association declaration of Helsinki. JAMA: The Journal of the American Medical Association. 2000; 284(23):3043–3045. [PubMed: 11122593]

What is already known about the topic?

- People with dementia are at risk for under treatment of pain
- A paucity of research exists regarding pain in people with dementia
- People with dementia are often excluded from research

What this paper adds

- Using pain as an exemplar, this discussion provides a method to address ethical and legal issues in research in people with dementia
- This paper provides several examples for overcoming many institutional barriers to conducting pain research in people with dementia