Conducting Research Related to Treatment of Alzheimer's Disease: Ethical Issues

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Abstract:

Researchers are obligated to protect the rights of study participants. Protecting the rights of patients with Alzheimer's disease (AD) is particularly complicated because of the special needs of this patient population, and the characteristics of developing treatments and technologies. Respecting autonomy and the right to self-determination are complicated by difficulties associated with assuring competence, understanding, and voluntariness in the informed consent process. Protecting patients with AD from harm may be complicated because new treatments have subtle side effects that may be difficult to detect in patients experiencing communication difficulties. Harm to patients with AD also may occur from withholding proven treatments in placebo-controlled trials, and in the use of genetic testing. Issues of justice in the allocation of research dollars and the ability of patients with AD to participate in research are also discussed. By recognizing potential pitfalls, researchers involved in testing new treatments for patients with AD can take proper steps to assure ethical treatment of study participants.

Article:

Alzheimer's disease (AD) is a condition characterized by progressive neurologic degeneration, resulting in gradual deterioration of memory, language, judgment, and affect. Alzheimer's disease usually begins around age 60, but onset may occur as early as age 40. The disease currently is estimated to affect more than 4 million Americans, with 250,000 new cases diagnosed each year. Because of longer life expectancy and the aging of the "baby boomer" population, 14 million Americans are expected to have AD by the year 2050—an immense social and economic burden for the next generation (American Health Assistance Foundation, 2000).

There is hope that recent advances in basic and pharmacologic sciences will result in effective treatments for AD. The National Institutes of Health and the pharmaceutical industry have invested significant resources in developing new chemical compounds to treat the symptoms or slow the progress of AD, and genetic research may result in treatments to prevent the disease altogether. The need for testing these products has and will continue to produce a great demand for clinical trial participants.

The participants in medical research are vulnerable in a number of ways. First, medicine is a very complex field, which is not easily understood by the average person. Study participants often have neither sufficient knowledge to determine the best course of action for treating or preventing a disease, nor sufficient knowledge to ascertain whether participating in research is unduly dangerous. They are dependent on clinician researchers to advise them correctly.

A second source of vulnerability is a function of the fact that study participants are often patients who have a problem for which they are seeking treatment. These participants place their lives in the hands of clinician researchers, trusting they will act in the participants' best interests. Third, because clinical research often takes place in a health care setting, researchers are able to obtain sensitive information that may place study participants at social or economic risk, such as the presence of diseases that could affect productivity and, hence,

employability and insurability. Fourth, clinician researchers, by virtue of their expertise and socioeconomic status, may be intimidating to patients. Patients may hesitate to exercise their autonomy and, consequently, acquiesce to all that is requested of them—even when it may not be in their best interests.

Because of these and other recognized vulnerabilities, several codes of ethical standards have been developed related to the appropriate treatment of human participants in research. These include the Nuremberg Code, the Declaration of Helsinki (World Medical Organization, 1996), and the Belmont Report (Harrison, 1993; Lurie & Wolfe, 1999; Shuster, 1998). These codes outline the rights of human participants of research, which can be summarized into the following three ethical principles:

- Respect for persons.
- Beneficence.
- Justice.

These rights, in turn, imply responsibilities on the part of researchers. The researcher's job of protecting the rights of participants who have AD is complicated by the complexity of the disease, that AD results in progressive neurologic deterioration, and the nature of available diagnostic tools and treatments. This article focuses, in depth, on the particular responsibilities and challenges faced by investigators in protecting the rights of study participants with AD.

RESPECTING RESEARCH PARTICIPANTS

Respect for the person requires the researcher to acknowledge the dignity and autonomy of individuals. It also requires that individuals with diminished autonomy or those who may not be able to speak for themselves (e.g., live human fetuses, children, prisoners, the mentally disabled, and those with severe illnesses) receive extra attention to be sure their rights are protected. The principal way the dignity and autonomy of participants in research is honored is through the use of full informed consent. There are five basic elements of full informed consent (Faden & Beauchamp, 1986):

- Disclosure of information.
- Comprehension.
- Voluntariness.
- Competence.
- The decision to participate or not participate.

Disclosure and Comprehension

Disclosure means participants must receive adequate information about the nature of the study, what they will experience, the risks associated with the experimental treatment, and whether or not they can expect to experience any benefits as a result of the study. Participants also have the right to know what treatments are available to them if they do not participate in the study. Comprehension means the researcher has an obligation to ensure, to the greatest degree possible, participants understand what is disclosed. Voluntariness means participants have been told they have the right to refuse to participate, or to withdraw from the study at any point without fear of retribution. The decision to participate or not participate involves the actual authorization to include the patient in the study.

The informed consent process can be complicated with patients with dementia. In the early stages of AD, neuronal damage primarily affects the hippocampus of the brain. The hippocampus function in the acquisition of information stored in long-term memory, and is responsible for transferring recent experiences into long-term memory. In recruiting a patient with early AD into a study, the investigator may find that the patient appears to comprehend disclosure of the various aspects of the study. However, they may quickly forget what was discussed, including that they consented to the study. The researcher must also remember that informed consent is an ongoing process in which the investigator re-evaluates, over time, the willingness of participants to continue with a study. However, as discussed in more detail below, ongoing consent in AD patients is complicated by the

progressive mental deterioration that occurs with the disease. In patients who are gradually becoming incompetent, it is not clear how changing preferences should be honored.

Voluntariness

With informed consent, investigators have an obligation to assure that participation is voluntary. Various approaches exist to obtain consent to participate in a study. To convince, by providing facts and permitting the patient to decide based on those facts, is referred to as persuasion. Persuasion is acceptable as long as it is clear to the participant that they have a right to refuse. Coercion, manipulation, deception, indoctrination, and seduction may result in patient decisions not consistent with the patient's considered judgments. These behaviors are considered unethical (Faden & Beauchamp, 1986).

Because the competence of AD patients is often questioned, researchers may choose not to approach the participant for consent. Instead, they may proceed directly to a family member or other legal guardian for authorization to include the patient in the study. Evidence suggests, despite the disease process, people with AD still have personal values that investigators should respect. Researchers should refrain from "talking around" the patient as if they do not exist. Such conduct precludes voluntariness, and is demoralizing to patients struggling to maintain their autonomy.

According to the Ethical Guidelines established by the Alzheimer Society of Canada, "while still capable, the individual should be given choices and the opportunity to make decisions" (Fisk et al., 1998, p. 244). These guidelines suggest techniques that can be used to make the decision-making process simpler for patients with AD, including reducing the number of options presented and reducing more complex decisions into a series of simple decisions with step-by-step guidance through the stages (Fisk et al., 1998, p. 244).

Competence

Competence usually refers to a legal definition of whether the person has the legal right to make important decisions. Children younger than 18 are not of legal age to sign an informed consent. Individuals who have mental illness or significant cognitive disorders (e.g., AD) may be determined incompetent in formal legal proceedings. If a person is deemed legally incompetent, the researcher is obligated to obtain legal consent from the next of kin (e.g., spouse, parent, children, siblings), or a legally designated proxy. The proxy participates in the consent process, and should be guided by their beliefs regarding what the patient would want if competent to provide consent. Although the proxy may legally provide the consent, the researcher is ultimately responsible for assuring that decisions made by the third party are contrary neither to the patient's wishes, nor to the patient's best interests (Fisk et al., 1998).

Decision to Participate

In discussing the actual decision to participate or not participate in a clinical study, some ethicists argue that the researcher has an obligation to be certain that the decision is "authentic" (Faden & Beauchamp, 1986). Authenticity is a difficult term to define and, perhaps, is best illustrated by providing an example of a behavior that is not authentic. The following is a hypothetical example of a consent.

Mr. Z is asked to participate in a study to test a new therapy for AD. The new treatment involves gene therapy. The researcher describes the study protocol, risks, benefits, and alternative therapies to Mr. Z and his daughter. Mr. Z agrees to participate. He appears to be acting intentionally and to clearly understand the nature of the study. No coercion is involved. However, Mr. Z's daughter advises the researcher that Mr. Z had always expressed strong moral concerns related to genetic manipulation and his religious beliefs precluded such therapies. Mr. Z's consent was not consistent with his prior expressed values.

Authenticity is particularly problematic when questioning patients with AD. The type of progressive deterioration occurring with the disease eventually renders patients unable to possess reflectively held values. Thus, it is quite common for patients with AD to behave in a manner that is "out-of-character." Some have suggested using

advanced directives, completed while competent, to determine if individuals may be used as participants in dementia research. However, serious problems have been raised with this proposal (Berghmans, 1998).

Ethicists disagree about what researchers should do in situations such as these. According to Dworkin (1993), the best method of respecting Mr. Z's autonomy is to adhere strictly to his earlier wishes, expressed when he was still competent. By doing so his personhood is respected as it was, when still intact. However, Dresser (Dresser, 1986) asserts that decisions affecting a demented person at a given time must speak to the person's current point of view. Dresser would argue that Mr. Z has a right to change his preferences. Jaworska (1999) seeks a middle ground between these two positions—stating that, despite cognitive deterioration, it may be possible with some patients to assess the extent to which new and seemingly inconsistent preferences are actually newly formed preferences. Careful questioning of Mr. Z by his daughter may determine the reason for his change in values. The consistency of expressed preferences may also provide some clues regarding the extent to which they reflect internally held values. If Mr. Z changes his mind frequently about his willingness to accept gene therapy, the researcher may be able to assume with some certainty the best way to respect Mr. Z's wishes is to honor his preferences expressed when he was still competent.

Some clinician researchers advocate that, when completing advanced directives, patients indicate their willingness to participate in research protocols and identify a proxy who can make such decisions for them in the event that their competency is diminished (Sachs, Rhymes, & Cassel, 1993). Proxy or caregiver involvement is also important from the perspective of adherence. As the disease progresses, researchers will increasingly rely on others to be certain that the experimental protocol is followed (Fisk et al., 1998).

BENEFICENCE

Researchers are required to protect the welfare of participants. This directive usually takes the form of two moral principles. The principle of nonmaleficence instructs agents not to cause harm to others. Precepts against killing and assault are based on this principle. The principle of beneficence counsels agents to promote the welfare of others. Others' welfare can be promoted by preventing evil or harm, removing existing evil or harm, and positively promoting the welfare of others (Faden & Beauchamp, 1986). Four areas in which beneficence is a particular issue in AD research are:

- When research is not expected to provide direct health benefits for the participants (i.e., nontherapeutic).
- Risks associated with new pharmaceutical treatments.
- Use of placebos in clinical trials.
- Use of genetic tests to screen for risk of AD.

Direct Health Benefits for the Participants

Because researchers handle experimental drugs or treatments, they are often unaware of all of the risks involved. Thus, by administering experimental treatments, researchers may cause unforeseen harm. Researchers are obligated to guard against potential harm by making their best efforts to identify possible adverse events, and determine the probability that participants will encounter such events. This is conducted through Phase I studies, when available, or through careful review of the literature and consultation with clinicians and scientists who have knowledge about the drug or treatment under investigation. The researcher must then make a judgment regarding the extent to which the research goals sought justify the identified risks. In biomedical ethics literature, this is referred to as the "benefit–risk ratio" in which the investigator must weigh and balance probable risks and benefits to be gained from the research.

According to Faden and Beauchamp (1986), the researcher's obligation to "do no harm" is not a pledge never to cause harm to study participants, but rather to be certain the potential benefits to be gained by the research outweigh the risks involved. For all known and anticipated risks identified, the researcher is obligated to guard against potential problems. A research protocol should be developed including:

- Screening criteria eliminating individuals for whom the intervention would not be advised.

- Monitoring procedures for adverse events or side effects among study participants for as long as participants are deemed at-risk.
- Specific strategies for handling adverse events or side effects, such as criteria for dropping participants from a study or treatment plans for handling problems that arise.

Some institutions carry insurance to reimburse participants for adverse health events resulting from clinical investigations. Depending on the type of study, a Data Safety Monitoring Board (DSMB) may be formed. The DSMB consists of researchers and clinicians not affiliated with the clinical study. They provide oversight to the statistical, medical, and ethical aspects of the study through periodic review of interim data on trial performance, treatment safety, and treatment efficacy (Hawkins, 1991; Wittes, 1993).

Risks Associated with New Drugs

According to Whitehouse (1996), in considering the development of new drugs for AD it is helpful to think in terms of short-, intermediate-, and long-term approaches. The first category consists of drugs currently on the market for symptomatic treatment of AD. These include cholinesterase inhibitors such as tacrine, donepezil, and rivastigmine (Lemiere, Van Gool, & Dom, 1999; Rosler et al., 1999; Whitehouse, 1996). The intermediate category consists of compounds which delay the progression of the disease, including such drugs as selegiline, vitamin E, estrogen, and nonsteroidal antiinflammatory drugs (National Institute on Aging, 1997; Whitehouse, 1996). The long-term approaches include treatments to prevent or cure the disease, which may result from future discoveries pertaining to genetics and the molecular pathogenesis of AD (Whitehouse, 1996).

One of the primary ethical concerns pertaining to use of experimental drugs and treatments with patients with AD is the potential inability of patients with more advanced disease to inform researchers about adverse reactions or side effects they are experiencing. Many of the AD drugs currently used or being tested for treatment of AD have subtle side effects (e.g., headache, nausea, abdominal pain, muscle pain, hot flashes, breast tenderness) that may be difficult to detect. Side effects or adverse events are likely to be more difficult to detect in participants with significant communication problems.

Another potential problem associated with drugs for symptomatic treatment of AD was recently discussed in a letter to the editor of the Journal of the American Geriatrics Society (Bianchetti & Trabucchi, 1999). In this letter, Bianchetti and Trabucchi present the case of a 53-year-old woman with AD being treated with donepezil. Although the medication resulted in substantial improvements in intelligence and memory, the patient became distressed because she regained awareness of her declining physical and mental state. The authors were successfully able to treat the patient with antidepressants. However, this example demonstrates that current treatments may result in patients re-living the distress associated with AD-related decline, and careful attention must be paid assure that the patient's quality of life is not compromised.

Use of Placebos

Placebo-controlled trials are common in testing new drugs (Burstein & Swiontkowski, 2001). However, there is current debate about the ethics of using placebos in treatment studies where proven therapies exist for treating the disease under study (Macklin, 1999; Rothnan & Michels, 1994). The original wording of the Declaration of Helsinki states:

> in any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists (World Medical Organization, 1996).

However, revisions to the Helsinki document have been proposed pertaining to the use of placebos. Article 18 of the revision permits the use of a placebo in cases where it is "justified by a scientifically and ethically sound research protocol." The proposed revisions further state that "when the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency" (Brennan, 1999, p. 529). Levine argues in favor of the revised language, stating that the original Helsinki document

precludes the development of all new treatments, except for those diseases for which there are no proven therapies, and use of placebos is justified on the grounds of efficiency (i.e., that requiring active treatment in control groups would substantially increase the expense of conducting studies on new therapies). He states that the use of placebos is justified in cases where the adverse effects of withholding an agent are merely symptomatic and rapidly reversible. He further argues that another justification for use of placebos is they are responsive to the patient's right to self-determination (i.e., that normal volunteers have the right to assume risks that they perceive to be reasonable in the pursuit of science) (Levine, 1999).

Although such arguments may work for studies testing new treatments for the common cold, arthritic symptoms, or mild hypertension, in the future these arguments may not be useful in justifying research pertaining to AD treatments. Cholinesterase inhibitors provide only symptomatic relief and, thus, it may be justifiable to withhold these for the duration of a clinical trial. However, some of the intermediate drugs such as selegiline, vitamin E, nonsteroidal anti-inflammatory agents, and estrogen may delay disability. Alzheimer's disease results in progressive decline. As evidence mounts that these drugs alter the course of the disease it will become more difficult to justify withholding them, even under the proposed Helsinki revisions. This issue raises three questions:

- How much evidence is required questioning the use of placebos?
- What degree of societal benefit must be expected to justify the continued use of placebos?
- How should researchers balance to the harm done to individuals from whom proven treatments were withheld against the potential benefits to be realized from society?

Unfortunately, no clear answers to these questions exist.

In response to the argument that normal volunteers have the right to assume risks they perceive to be reasonable in the pursuit of science, it is important to note that patients with AD are not "normal volunteers." As stated previously, patient self-determination needs to be preserved and, in cases where proxy consent is legally required, assent should be obtained from the patient. Even if assent is obtained, it is doubtful that proxies have a right to volunteer vulnerable participants for studies contrary to their best interests. In placebo controlled trials, those participants randomized to the control group may be worse off than they would have been by not participating in the study—at least when a treatment with some known efficacy is available.

Genetic Testing

Genetic information pertaining to the risk of developing AD is another area of concern related to beneficence. The field of genetics is progressing rapidly, permitting early identification of risk for certain diseases, as well as the possibility of future gene-based therapies. In October 1993, a research group from Duke University reported the discovery of a genetic risk factor for susceptibility to AD. Shortly after this announcement, physicians were deluged with requests for the "Alzheimer test." One biotechnology firm (Genica, San Diego, CA) quickly produced marketing materials about the test, suggesting it could be used for early identification of patients who could benefit from early treatment or patients who could participate in clinical trials of new AD drugs (Quaid, Dinwiddie, Conneally, & Nurnberger, 1996).

According to Post et al. (1997), five professional groups have developed consensus statements related to genetic testing for susceptibility to AD. All agree that predictive testing in individuals who are asymptomatic is not recommended at this time, but differ on use of the test for diagnosis of symptomatic individuals. Regardless of how it is used, there are several ethical issues researchers must consider before using such a test. With the current state of knowledge, it is not possible to determine, definitively, whether or not an individual will develop the disease.

Being identified as at risk can have tremendous negative implications for individuals. There is currently no cure, and it is not clear if anything can be done to reduce the test recipient's risk of developing AD. Anticipation of developing AD can diminish subsequent quality of life, and even result in suicidal behavior. A positive test can

also negatively influence employability and insurability Thus, it is not clear that the benefits of genetic testing outweigh the risks involved (Fisk et al., 1998). Genetic testing of individuals who have a family member with AD is appropriate if requested, and if it is accompanied by pre- and post-test counseling (Post et al., 1997).

JUSTICE

The principle of justice refers to whether or not a person has been treated according to what is fair, due, or owed (Faden & Beauchamp, 1986). Justice demands the burdens and benefits of research to be distributed fairly among all in society. Thus, no group should be unduly deprived of the benefits of scientific research, nor should any group be disproportionately burdened. Patients with dementia are frequently excluded from research out of concern for exploiting vulnerable participants. However, according to Post et al. (1997), to deny access of patients with AD to participation in clinical research is to avoid rather than accept and practice ethical responsibility. If extra attention is paid to issues of respect and beneficence, these vulnerable participants can and should be recruited into clinical studies. To do otherwise would greatly impair society's progress in treating AD.

Research is very expensive. These expenses are undertaken because of expected societal benefits. However, the manner in which research dollar allocations are made often has very little to do with the extent to which a particular health problem is a pressing societal issue. Rather, the amount of money spent on a disease is often a function of the biases of policymakers, and also the need for policymakers to respond to the will of their voting constituents.

For example, certain diseases seem to trigger more of an emotional response on the part of the public. Heart disease is the number one killer in the United States, but because cancer is more feared, far more money is spent on cancer research than on cardiovascular research. Some claim the voting power of an aging population is pressuring Congress to invest in AD research and, as a result, the National Institute on Aging is providing disproportionate research support in this area (Adelman, 1998; Wadman, 1998). However, given the tremendous economic burden of AD and the aging of the "baby boomers," health care expenditures related to the disease are likely to increase greatly as this group peaks in number in the next 20 to 30 years. Recent estimates suggest new drug developments have the potential to offer cost savings for many patients, and suggest continued investment in AD research may be worthwhile (Knapp, Wilkinson, & Wigglesworth, 1998).

SUMMARY

Nurses are often involved in AD research as investigators, study coordinators, or data collectors. In these various roles, nurses have a responsibility to assure that patients receive the respect they are due, that patients are not harmed, and that the benefits and burdens of research are distributed in an equitable manner. As discussed in this article, protecting the rights of patients with AD who participate in research is particularly complicated because of the special needs of this patient population, and the characteristics of developing treatments and technologies. By recognizing potential pitfalls, nurses involved in AD research can take proper steps to assure ethical treatment of study participants.

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